The diagnosis of deep venous thrombosis

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Proefschrift

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To those who have been working for a better world to live in, while I was selfishly writing this thesis.

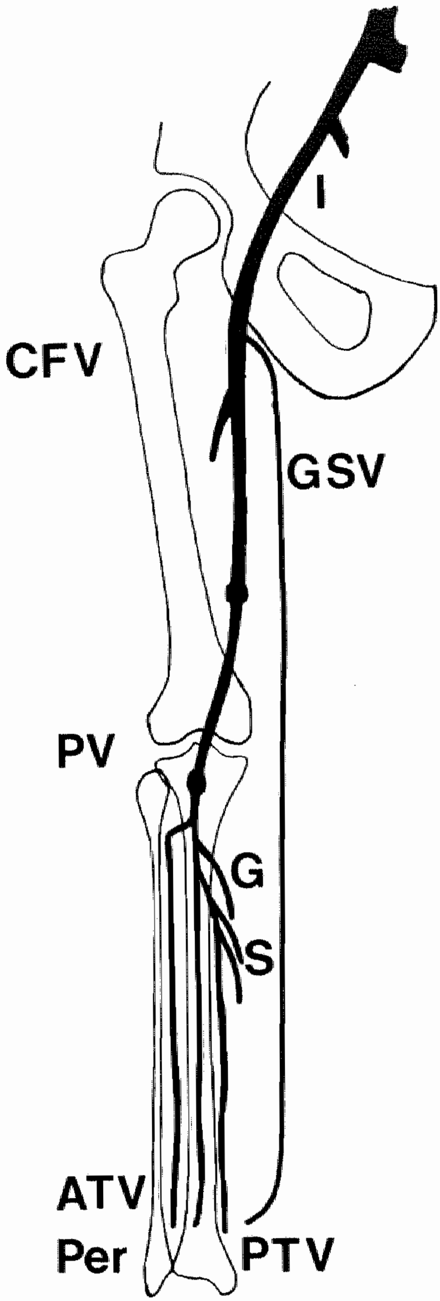
Contents

I. Introduction

One of the major problems in the management of thrombo-embolic disease is the inaccuracy of the clinical diagnosis. Physical examination is neither sensitive, nor specific. Many cases of DVT remain undetected until pulmonary embolism (PE) or venous hypertension ensues. On the other hand, many diseases can mimic the clinical picture of DVT. When venography is performed in patients with a clinical diagnosis of DVT, half of them appear not to have any thrombus at all.
If one were to rely on the clinical diagnosis, half of the patients would be treated unnecessarily with anticoagulants, while they are witheld from others in need of them.
Untreated DVT is associated with a considerable morbidity and mortality due to the post-thrombotic syndrome and pulmonary embolism. Treatment with anticoagulants, however, is associated with significant morbidity and mortality due to haemorrhage.The gradual awareness of the limited accuracy of clinical signs and symptoms initiated the search for additional diagnostic methods. At least 38 different tests and examinations have been described [204] indicating that the ideal method still has to be found.
Röntgen contrast venography is generally regarded as the "Gold Standard" with which all other methods should be compared. Because it is disturbing to the patient and bears the possibility of adverse reactions, the venogram is unsuitable as a routine examination. Favourable reports have appeared on non-invasive examinations, such as Doppler ultrasound and venous outflow measurement. Both methods combine a high accuracy with low costs and a lack of undesirable side effects.
Unfortunately both performance and interpretation of these tests are subject to significant variations.
It is the aim of the present study to evaluate which criteria of the venous Doppler examination and venous outflow measurement are most accurate, and to determine whether these tests are suitable to make therapeutic decisions.
In order to quantify the venous Doppler signal a number of test subjects and patients with documented DVT have been examined with the aid of spectral analysis. In other test subjects the influence of various circumstances on the result of venous outflow measurement has been examined.
In a prospective study consecutive patients with a clinical diagnosis of DVT have been examined with both Doppler ultrasound and venous outflow measurement, the results of which are compared with venography.
The significance of different alterations of the venous Doppler signal is evaluated. Discriminant analysis is performed for various parameters of venous outflow measurement.
A cost benefit analysis is made for different diagnostic regimens.
Finally, an algorithm is proposed for the management of patients with clinically suspected DVT.

2.2:1

Anatomy of the venous system as it appears on Röntgen contrast venography. In the leg, three paired crural veins and the muscular veins are present, which join into the single popliteo-femoral vein. The superficial greater saphenous vein acts as a collateral when the deep veins are occluded.



I	Iliac vein
CFV	Common femoral vein
GSV	Greater saphenous vein
PV	Popliteal vein
G	Gastrocnemius group
S	Soleal vein
ATV	Anterior tibial vein
Per	Peroneal vein
PTV	Posterior tibial vein

II General aspects of Deep Venous Thrombosis

2.1 Origin of deep venous thrombosis

The classical triad on the origin of DVT was postulated by Virchow more than a century ago [265]. This triad can be translated into current biochemical and patho-physiological knowledge, without loosing its significance; venous stasis, endothelial injury and hypercoagulation are still regarded to be major causes of DVT.

Clinical observations have shown that DVT usually arises from the valve pockets in the calf veins [104, 185, 193, 222, 223], which is the site where stasis is most pronounced [65, 156, 186]. Additionally thrombosis frequently occurs during conditions of impeded venous flow like anaesthesia [32, 156], paralysis [91, 272], circulatory impairment [45] and prolonged sitting [117, 233].
Endothelial lesions, either hypoxic [102], chemical [115] or mechanical [6, 74, 236], have been shown to induce local thrombus formation.
Hypercoagulation indicates a shift in the equilibrium between clot formation and clot resolution towards the former situation. This shift can be accomplished in many ways. Thrombocytosis is associated with an increased incidence of DVT, particularly in myeloproliferative disease [198].
Increased levels of activated clotting factors are induced by the release of tissue thromboplastin in trauma and surgery [198], or by thromboplastin like substances released by malignant tumours [200].
Decreased levels of circulating inhibitors of coagulation will have a similar influence. Inherited deficiencies of antithrombin III, protein C, protein S and others have been described, all resulting in serious thrombo-embolic disease in younger patients [24, 36, 38, 47, 67, 94, 263].

A clot removing (fibrinolytic) system was described by Mc Farlane in 1948 [165]. The normal fibrinolytic activity is decreased during the first three postoperative days, in which 69-94% of all postoperative thrombi are first detected [32, 144, 275].
Defective fibrinolysis has been observed in the blood and vein walls of patients with "idiopathic" venous thrombosis [129].

2.2 Venous anatomy of the lower extremity

The venous system of the lower extremity is commonly divided into 3 systems:
-superficial veins
-perforating veins
-deep (subfascial) veins
The main vessels of the superficial system are the greater and lesser saphenous vein. The greater saphenous vein emerges from the medial border of the foot, with a constant localisation anterior to the medial malleolus and running upward along the medial side of the limb, to the oval fossa, where it joins the common femoral vein.
The lesser saphenous vein emerges from the lateral side of the foot, running behind the lateral malleolus and upward dorsally of the calf, joining the popliteal vein at a variable level in the popliteal fossa. A network of superficial veins attends these two major truncs.
The surgical importance of these veins is primarily the use of the greater saphenous vein as an arterial substitute, indicating that they are not essential for venous drainage of the limb.
The perforator system consists of numerous vessels passing through the fascia of the leg, thus connecting the superficial to the deep system. The valves present allow blood flow in this direction only. Because of their large number – 155 with a constant localisation have been described [157] – occlusion of these veins is not of clinical importance. Valvular incompetence

of these veins, however, will cause serious venous hypertension, finally resulting in a crural ulcer.
The deep veins of the leg emerge from the foot and are usually paired, running as venae comitantes with the three crural arteries. At the level of the ankle the posterior tibial veins (PTV) are the most pronounced, as they drain the extensive rete venosum of the sole of the foot. The PTV runs directly behind the concomitant artery, which can be palpated behind the medial malleolus. More proximally the soleal and gastrocnemius veins drain into the PTV. The dorsum of the foot drains through the dorsal pedal vein into the anterior tibial veins (ATV). These veins course upward directly anterior to the interosseus membrane between tibia and fibula. They can easily be recognised by their right angled deflection toward the popliteal vein. The peroneal veins run along the medial crest of the fibula, joining the PTV proximally. The popliteal vein (PV) is moulded by the confluence of the crural veins in the proximity of the knee joint. In the lower part of its course it is medial to the popliteal artery, gradually passing superficially from the artery to a posterolateral position. The popliteal vein changes into the superficial femoral vein (SFV) at the opening in the adductor magnus. The popliteo-femoral vein is duplicated in 3-5% of the cases. At about 4-12 cm below the inguinal ligament, the SFV and deep femoral vein join into the common femoral vein (CFV), which is medial to the artery. On functional grounds, the external iliac vein starts after the confluence of the CFV and the greater saphenous vein (GSV). The pelvic viscera drain through the internal iliac vein, which joins the external from medial, to form the common iliac vein (CIV). The left and right iliac veins join together to form the inferior vena cava. The left CIV is crossed by the overlying right common iliac artery, the pulsations of which cause intimal reaction and "spur" formation in approximately 20% of the subjects in autopsy studies [68, 161].

Anatomical description was derived from Gray's Anatomy, Ed. Warwick R, Williams PL. Longman 1973, and Die Flebografie der unterem Extremität, Ed. May R, Nissl R , Georg Thieme Verlag Stuttgart 1973.

2.3 Deep "Phlebothrombosis" versus superficial "Thrombophlebitis"

From a clinical point of view, disease involving the superficial veins should be distinguished from disease affecting the deep venous system. Thrombus formation in the superficial veins is usually accompanied by a vigorous inflammatory reaction, causing clot adherence to the vessel wall. As a consequence, these thrombi rarely dislodge as an embolus. Occlusion of the superficial system does not interfere with venous drainage of the leg, and postthrombotic sequelae are not to be expected.
In contrast, large floating thrombi can arise in the deep veins, giving rise to life threatening pulmonary embolism. Occlusion of the deep veins and destruction of their valves will cause serious impairment of the venous circulation.
For these reasons superficial "thrombophlebitis" and deep "phlebothrombosis" are essentially different, each requiring their own particular approach [110, 194].

2.4 Incidence

In the Netherlands 20.200 patients are known to have been treated for DVT in 1984, accounting for a prevalence of 1.4‰. (Courtesy of the Federatie van Nederlandse Trombosediensten). In the Eindhoven district the number of patients treated for DVT dropped from 367 in 1981, to 143 in 1984, accounting for a prevalence of 0.97‰ and 0.38‰ respectively (jaarverslag Trombosedienst Eindhoven 1981, 1984). Males are affected in an equal frequency as females [141, 193, 196, 285], the incidence increasing steadily with age [141, 193].
Occasionally DVT occurs in childhood [286] and in symptomatic patients, younger age is not a reason to reject the diagnosis [141].

2.5 Sequelae

The significance of DVT is determined by its sequelae; the short term occurence of pulmonary embolism (PE) and the deleterious long term effects of the postthrombotic syndrome (PTS). Pulmonary embolism can be demonstrated in 0-33% of the patients with limited calf vein thrombosis, increasing to 53-62% in patients with proximal extension of the thrombus [143, 175]. The mortality rate of untreated PE is estimated to be 30%, declining to 8% when appropriate treatment is instituted [58]. According to death certificates, 2516 people died from PE in the Netherlands in 1981 (Courtesy of CBS).
Thrombosis causes an inflammatory reaction and valve destruction of the involved veins [65, 154].
Even when recanalisation takes place, valvular incompetence remains, resulting in venous hypertension [227]. As a result, the patient is troubled by persistent edema, an aching sensation, induration of the skin and in advanced cases by a crural ulcer [109]. After 2-3 years of follow-up on patients treated with Heparin, postthrombotic complaints are reported to occur in 14-79% of these patients, an ulcer is present in 5-16% of them [74, 79, 82]. In the general population, PTS is observed in 0.5-3.0% of the examined subjects [109, 176, 232], and causes an estimated loss of 2.000.000 working days/year in the United States [41].

2.6 Treatment

Until the 1940s, one could do nothing to treat DVT, but to wait until the symptoms subsided. In 1934 Morawitz stated: "Je weniger aktiv die Therapie um so besser. Viel Geschäftigkeit schädet" (quoted from Ziliacus) [293].
A dramatic change in the treatment of DVT occurred with the clinical introduction of heparin by Murray and Crafoord in 1936 [51, 181, 182], and of the coumarins by Butt in 1941 [4, 5, 12, 44]. Figures from 19 Swedish hospitals collected by Ziliacus showed a decline in the occurrence of PE during the course of DVT from 59/214 (25%) in untreated to 8/576 (1.3% in heparin treated patients. The indicence of fatal PE decreased from 20/214 (9.3%), to 3/576 (0.5%) in heparin treated patients [293]. Hospital admission for DVT was reduced from an average of 56 to 12 days. Presently the mainstay of therapy is intravenously administered heparin followed by a course of oraly administered coumarins[76, 121, 124, 126].
In this way extension of the thrombus is prevented, without removal of the thrombus itself [225].
In order to preserve the valvular function, fibrinolytic therapy or thrombectomy can be considered in selected patients [92, 203, 241].

Despite their beneficial effects, anticoagulants should be used with caution. Major bleeding due to coumarins is reported to occur in 4.3% per year of treatment [79], and heparin ranks fourth in drug induced deaths [205] with a reported mortality rate of 1 per 1000 treated patients [48].
During pregnancy coumarins will pass the placenta and have an established teratogenous effect [98, 240, 273].

III Diagnosis of deep venous thrombosis

3.1 Venography

3.1.1 Historical notes

A precurser of modern angiography was the projection on a Röntgenscreen of a projectile moving up and down in a human heart, observed by Trendelenburg in 1902 (Quoted from Franck [82]). Similarly Riethus introduced particles into the jugular vein of a dog and observed them move through the heart into the pulmonary circulation [82].
In the search for liquid contrast, quicksilver proved unsuitable because of its high specific gravity which inhibited its motion with the bloodstream. Drops of Bismuth oil were more useful and have been observed moving from the femoral vein, through the right side of the heart, into the pulmonary circulation, where it caused lethal embolism.
Berberich [21] succeeded in depicting peripheral veins and arteries in humans, using "Strontium Bromatum", which had no immediate ill effects.
Having a broad experience with arteriography, dos Santos [217] investigated the clinical application of phlebography, using an organic jodide compound: Per-Abrodil.
After a report on radiological evidence of axillary vein thrombosis by Veal [262], Frimann-Dahl [86] and dos Santos [217] were the first to publish on the venographic diagnosis of DVT in the lower extremity in humans.
In the following years, venography became a recognised method of investigation in the management of DVT [15, 16, 64, 158]. For some time the method fell into disrepute, due to problems with its interpretation [26].
A revival occurred with the modifications described by Lea Thomas and Rabinov which presently constitute the standard technique [152, 206].

3.1:1

Filling of the deep venous system with contrast is partly accomplished through the superficial system.

3.1.2 Performance of venography

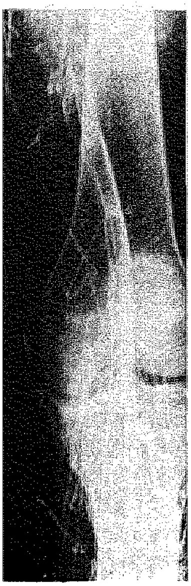
In order to prevent layering of contrast on the blood stream, the patient should be examined in a predominantly upright position, for which a tilting table is required.
The extremity to be examined should be completely relaxed and thus non-weight bearing. This is accomplished by placing a box under the non-examined leg. Additionally, to relieve the calf muscles, a rolled towel can be placed under the Achilles tendon of the examined limb.
A superficial vein, medial on the dorsum of the foot, is punctured with a 19-21 gauge butterfly needle. In view of the large capacity of the veins of the lower limb (300-700 ml), a sufficient volume of contrast should be injected, usually 75-125 ml but in some cases up to 250 cc may be required [26].
Fluoroscopic monitoring with a TV intensifier is used to achieve optimal imaging of each venous segment. Filling defects, due to insufficient contrast injection, dilution and streamlining may thus be prevented [152].
A tourniquet applied at the ankle is advocated by many authors in order to divert flow of contrast into the deep veins [152, 185, 210]. This is regarded as unnecessary by others, because the normal venous flow is directed from the superficial to the deep veins. (fig 3.1:1) Moreover, a tourniquet may prevent filling of parts of the deep veins and directly compress the anterior tibial vein, thus causing artifacts, suggestive of DVT [26, 206]. Under fluoroscopic control, AP and lateral films of the calf and knee are obtained, as well as an AP film of the thigh and inguinal region [26, 206]. The pelvic veins are depicted by tilting the table to a horizontal position and elevating the limb, while the femoral vein is compressed. On release of the compression the iliac vein is sufficiently filled with contrast and a picture is immediately taken [180, 206]. When this manoeuvre does not result in an opacification of the iliac vein and when the inferior vena cava is to be studied, direct puncture of the femoral vein can be performed [149, 152, 206].
When the venographic examination is completed all the contrast should be cleared from the limb. This is achieved by elevation, active muscle contractions [26] and by flushing with saline [152, 234] or a heparin solution [163, 173].

3.1.3 Interpretation of venography

The criteria for DVT as outlined by Rabinov [206] are as follows:

- The most reliable indication of DVT is a filling defect in the contrast, which is present in multiple views. When the thrombus is elongated the so-called "tram tract" is demonstrated because of the contrast being present at both sides of the thrombus. (fig 3.1:2)
- Abrupt termination of the column of contrast, which occurs at a constant level on consecutive images. (fig 3.1:3)
- Non-filling of a part of the deep venous system when a sufficient amount of contrast has been administered. (fig 3.1:4)
- Diversion of flow, representing collateral circulation around the site of venous occlusion.(fig 3.1:5)

Apart from demonstrating the precise extent of DVT, venography can also be used as an aid determining the duration of the disease.
In the initial stage a loose thrombus will be present for approximately 7 days. Adherence and retraction of the thrombus occurs from 7-21 days. Longterm follow-up will show either recanalisation with irregular vessel lining, or complete occlusion with collateral flow [151].
With the use of the technique described above, venography is now generally recognised as the "Golden Standard" in the diagnosis of DVT, with which all other methods should be compared to determine their accuracy [26, 76, 88, 124].
The validity of this approach was demonstrated by Hull [125] by means of long-term clinical follow-up of patients with a normal venogram.

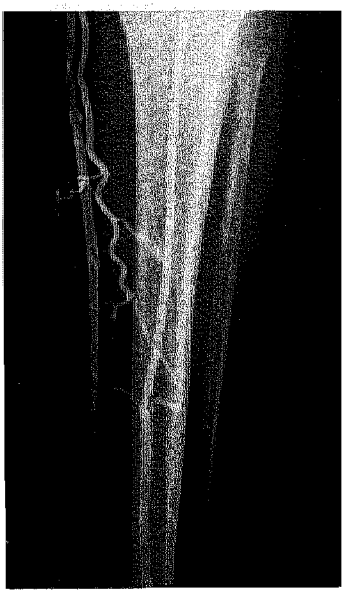


3.1:2

Persistent filling defect due to a thrombus in the superficial femoral vein.
The elongated thrombus causes the appearance of a tram tract or railway.

3.1:3

Abrupt stop of a column of contrast (←) which remained on the same level in serial projections. Persistent filling defects can be seen in several other veins.



3.1:4

Non filling of the deep venous system despite administration of a sufficient amount of contrast. The superficial greater saphenous vein acts as a collateral. Interruption of contrast in this vessel is caused by the valves present.

3.1:5

Superficial flow through superficial and pudendal veins in a patient with complete occlusion of the femoral and iliac veins.

3.1.4 Side-effects of venography

There are several reasons which make the "Golden Standard" for the diagnosis of DVT less suitable as a routine examination for all patients in whom DVT is suspected.
First of all it is an invasive procedure and the performance is impossible, for technical reasons, in approximately 10% of the patients [100, 199].
Injection of dye was experienced as painful in 59% of cases treated with plain and 30% of the cases when diluted dye was used [25].
Extravasation of the dye may result in an ulcer at the injection site [20], and in one case with a compromised circulation, gangrene occurred for which amputation of the extremity was required [150].
Intravascular administration of contrast media is associated with the occurrence of adverse reactions such as urticaria, bronchospasm and hypotension, sometimes leading to circulatory collapse. In a large prospective study, adverse reactions occurred in 5% of the patients and were fatal in 18/302.083 (= 0.006%) [224].
Contrast material is also known to be nephrotoxic. Subclinical acute renal damage was observed in 2% of the patients with a previously normal renal function and in 30% of the patients with pre-existent renal dysfunction [70].
Most importantly, venography is not only capable of detecting, but also of inducing DVT. The syndrome of postvenographical pain and swelling of the investigated limb was first reported by Homans [115] and was reported to occur in 24% of the patients examined with standard Renografin 60, and in 7.5% of the patients in whom diluted contrast had been used [25].
Objective evidence of DVT, by means of the fibrinogen uptake test (FUT), disclosed an increased uptake in 26-33% of the cases after venography with ionic contrast (Methylglucamine Iothalamate =Isopaque), compared to an incidence of 2-7% when a non-ionic contrast medium (Metrizamide = Amipaque) had been used [2, 22, 147].
As a consequence, the cost of this investigation would become an increasing objection to performing it, if more expensive non-ionic contrast media were to be used exclusively. However, flushing with a saline solution containing 10,000 U of heparin, resulted in a decline to a number of 3.3% of positive FUT scans after venography with an ionic contrast medium (Methylglucamide Iodamide) [173]. When care is taken to shorten the procedure as far as possible, to evacuate all the contrast after termination of the procedure and by additional flushing of the veins with heparin, venography can be performed with a minimum of ill effects.

3.1.5 Conclusions

Venography is the most accurate and, therefore, valuable method in the diagnosis of DVT. However, because of the possible adverse reactions it should be reserved for scientific purposes and for those patients in whom an unequivocal diagnosis is not obtained by other means.

3.2 Clinical diagnosis

3.2.1 Classical symptoms and signs of DVT

In the past, the diagnosis of DVT was confined to the classical symptoms and signs of the physical examination. There is, however, no classical study in which these symptoms and signs are outlined clearly. In order of frequency, the following symptoms are mentioned in 12 papers on the subject: [3, 54, 97, 106, 132, 148, 167, 171, 174, 196, 235, 256].

Calf tenderness	12 x
Edema or swelling	12 x
Homans' sign	11 x
Spontaneous calf pain	8 x
Altered skin temperature	7 x
Venous dilatation	7 x
Colour changes (erythema)	6 x
Lowenbergs sign	3 x
Increased calf firmness	2 x
Unexplained fever (Michaelis sign)	2 x

Homans' sign is ellicited by passive dorsoflexion of the foot, with the knee held in flexion [116]. The Lowenberg sign consists of increased calf tenderness when a congestion cuff around the thigh is inflated to 90-150 mm Hg for 5 minutes [160]. These signs and symptoms can be considered to be the classical appearance of DVT.

3.2.2 False negative results

Clinicians have long been aware that thrombosis may occur without these signs being present [114, 116]. It appeared from autopsy studies that a diagnosis of DVT had not been made in 90-95% of the cases with pulmonary embolism [18, 49, 239, 274]. With the development of the 125 I fibrinogen scan and its application in the screening of postoperative patients, it became apparent that DVT remains undetected in the majority of cases (Table 3.2:I).
From these figures it appears that DVT can be present in any subject with the slightest features compatible with this condition.

Table 3.2:I
Incidence of false negative results of the pysical examination, in patients with a positive 125 I fibrinogen uptake test.

Author		Number of patients with a positive scan	Patients with a positive scan, without symptoms or sings of DVT	
			No	percentage
Kakkar	1960	40	20	50%
Rosengarten	1971	26	17	65%
Kakkar	1972	62	32	52%
Hill	1972	53	44	83%
Browse	1974	61	41	67%
Harris	1974	56	51	91%
v.d. Linden	1975	33	24	73%
Borow	1981	96	87	91%
Veth	1982	44	35	80%
Feuth	1983	12	8	67%

3.2.3 False positive results

Thrombosis may not only be present in the absence of clinical signs, these signs may also be present in the abscence of thrombosis. This phenomenon was not appreciated for a long time because there was no method to confirm or reject the diagnosis. Bauer [15, 16] was the first to observe that normal venograms were obtained in approximately 20% of the patients with a clinical diagnosis of DVT. It was not until 1969 that the clinical diagnosis was challenged by Haegar [97]. Since then an increasing number of cases have been published showing normal venograms obtained in patients with a clinical diagnosis of DVT (Table 3.2:II).

From these studies it appears that an incorrect diagnosis of DVT is made in approximately one half of all cases. As a consequence, half of the patients will be treated for a disease they do not suffer from, if treatment is based solely on the physical examination. Some alterations in these figures can be observed in certain conditions. In patients recently subjected to surgery, DVT was present in 71% of the cases, as compared to 47% in non-operated patients [141]. In patients with 4 or more clinical signs, DVT was observed in 50-70%, as compared to 30-51% of the cases with fewer clinical signs [50, 97, 174, 235].

When single signs are reviewed it appears that their predictive value rarely exceeds 50% (Table 3.2:III).

Table 3.2:II
Incidence of false positive results of the physical examination in symptomatic patients. In patients with a clinical dagnosis of DVT, a normal venogram is obtained in approximately 50% of the cases.

Author		Number of patients with a clinical diagnosis of DVT	Number of patients with a normal venogram	
			No	Percentage
Philips	1963	22	10	45%
Haegar	1969	72	39	54%
Fossard	1974	822	389	47%
Cranley	1976	133 (limbs)	61	46%
Stamatakis	1978	812	411	51%
Nicolaides	1978	228	97	43%
O'Donnel	1982	79	43	54%
Molloy	1982	100	57	57%
Kierkegaard	1982	876	437	50%

Table 3.2:III
The positive predictive value of several 'classical' signs of DVT, when the result of the physical examination is compared to venography.

	Haegar 1969	Alexander 1974	Cranley 1976	Richards 1976	Cooperman 1979
Pain calf	30/60 = 44%	–	60/112 = 53%	–	–
Calf tenderness	28/57 = 49%	12/54 = 22%	59/103 = 57%	62/91 = 68%	17/50 = 34%
Skin temperature	11/22 = 50%	–	–	33/46 = 71%	8/14 = 52%
Ankle edema	25/55 = 45%	27/85 = 32%	65/121 = 53%	40/88 = 45%	17/49 = 35%
Calf edema	13/24 = 54%	–	–	–	–
Venous dilatation	9/15 = 60%	15/19 = 79%	–	27/36 = 75%	
Homans	11/19 = 58%	–	29/47 = 62%	42/58 = 72%	10/24 = 42%
Lowenberg	3/5 = 60%	–	–	37/56 = 66%	–
Erythema	–	16/29 = 55%	–	–	6/13 = 46%

3.3 Differential diagnosis

With the awareness that pain and swelling of a limb is just as often not caused by DVT as it is, interest was aroused in other conditions that could evoke the same clinical picture.
Numerous other conditions have been recognised in large series of patients in whom venography had rejected the diagnosis of DVT (Table 3.2:IV). Superficial phlebitis, the post-thrombotic syndrome, previous trauma and congestive heart failure are frequently observed in these patients. The ruptured Bakers cyst has been subject of particular attention. It has even acquired the indication of "pseudothrombophlebitis" [138].
A rupture of the Achilles tendon [90] and localised myositis [136] are other diseases of the locomotor tract, they are sometimes mistaken for DVT.
A 61 year old women has been reported with a 2-year history of swelling of the left leg, occurring after intervertebral disc surgery and resulting in ulceration of the left calf. Initially, a diagnosis of DVT had been made and PTS was a likely explanation for the subsequent complaints. After re-admission for supposed recurrent DVT, an aorto-iliac arteriovenous fistula was finally disclosed and corrected surgically [75].

The reverse situation, DVT being mistaken for another disease, is reported less frequently. Dos Santos [217] reported a patient with a painful calf which was at first attributed to arterial occlusion but it finally appeared to be DVT with arterial spasm. A 62-year old women has been described with peri-umbilical pain gradually moving to the right lower quadrant of the abdomen. Her body temperature was 37.5°C and the WBC on admission was 16.8 x 10^6/1. Previous Swan Ganz catheterisation through the right femoral vein was the clue to iliac vein thrombosis, instead of appendicitis [271].
In a 21 year old male with a traumatic laceration of the liver, a postoperative febrile episode was ascribed to abces formation, but it finally appeared to be due to thrombosis of the inferior vena cava. [6]

With our present knowledge DVT should be regarded as a treacherous disease. It may develop unnoticed until it gives rise to (fatal) PE. On the other hand it is mimicked by many other conditions which renders the clinical diagnosis unreliable.

Table 3.2:IV
The extensive differential diagnosis of DVT. The conditions mentioned were recognized after the initial diagnosis of DVT had been rejected by venography.

Diagnosis	Barnes 1975	Gross 1978	Hull 1981
Superficial phlebitis	–	16	–
Neuropathy	1	16	–
Postthrombotic syndrome	60	15	6
Arthritis condition	11	12	2
Trauma	37	8	9
Congestive hartfailure	56	8	–
Psychogenic	–	7	–
Cellulitis	17	5	3
Vasculitis	–	4	–
Arterial occlusive disease	4	4	–
Sickle cell ulcer	–	1	–
Muscle strain	–	–	21
Edema due to paralysis	7	–	8
Lymphangitis / obstruction	–	–	6
Muscle tear	–	–	5
Bakers cyst	1	–	4
External compression due to malignancy	36	–	–
Pregnancy	11	–	–
Chronic fatigue due to morbid obesity	4	–	–
Unknown	–	15	23

3.4 Doppler ultrasound

3.4.1 Historical notes

The Doppler principle consists of a change in the frequency of a wave pattern, when transmitter and observer move in relation to each other. Chilowski obtained a patent on a method of employing the Doppler principle for flow measurement in 1937. During the Second World War marine speedometers were developed using the Doppler principle (Quoted from Herrick) [105]. Ultrasound was used for flow measurements by Swengel [255], using the transit time technique. An acoustic wave is transmitted between two transducers, upstream and downstream alternately. Interference of flow velocity with acoustic wave velocity results in a phase of shift which is detected. The Doppler shift of ultrasound was put into clinical practice by Satomura [219], who developed an apparatus for transcutaneous blood flow measurement.

3.4.2 Mode of action

The necessary equipment consists of a high frequency oscillator, a receiver, transducer, and earphones. When the emitted sound is reflected by moving particles, the frequency of the reflected signal is changed according to the following formula:

$$df = \frac{2fe \cdot V \cdot \cos\alpha}{C}$$

Where
df = frequency shift
fe = frequency of the transmitted ultrasound
V = velocity of the reflecting object
α = angle between sound beam and flow direction
C = velocity of the sound in the medium being studied [137, 248]

Satomura did not only supply the apparatus, but also reported on different kinds of blood flow in the arteries of an extremity, the carotid artery and in the jugular and femoral veins. He thereby laid the foundation for extensive investigation of vascular disease. Franklin [84] showed the frequency of the reflected signal to be linearly related to flow velocity, both during steady and sinusoidal flow. In an experimental setting with a known flow velocity, measured and predicted (calculated) Doppler shifts were in agreement [238]. In a comparative study between commercially available instruments *(Versatone Bidirectional Doppler M-9, Sonicaid BV 380 Doppler, Parks 806B and 806C and Delande DUD 400)* all proved capable of measuring flow velocity within a range of 5% compared to an electromagnetic flowmeter [137, 226].
An improvement in velocity measurement was made by McLeod [168], through the introduction of a velocity meter that distinguishes between forward and reversed flow.
As can be seen from the formula, the frequency shift is proportional to twice the emitted frequency. As a result, low velocity flow is detected more accurately with a higher frequency of ultrasound. This principle is limited by the fact that absorbance of energy in tissue is proportional to the frequency [93]. The optimal frequency appears to be:

$fopt = 9/d$ Mhz

where d = the vessel depth in centimeters [209].

As a consequence, a frequency of 8 Mhz is commonly used for examination of superficial vessels [252] while 5 Mhz is more suitable for the popliteal and femoral veins [11, 63, 228, 244, 251]. Evans [71] was able to obtain signals from the iliac veins and the vena cava with a 2 Mhz instrument.
The Doppler shift is finally determined by the cos α, where α is the angle between the vessel and the beam of ultrasound. The optimal probe angle varies between 38° and 52° with different instruments [226].
A frequency shift of less than 200 cycles/sec. is filtered out [230, 238, 244]. Therefore, low velocity flow cannot be measured reliably with contemporary instruments [226].

3.4.3 Clinical application

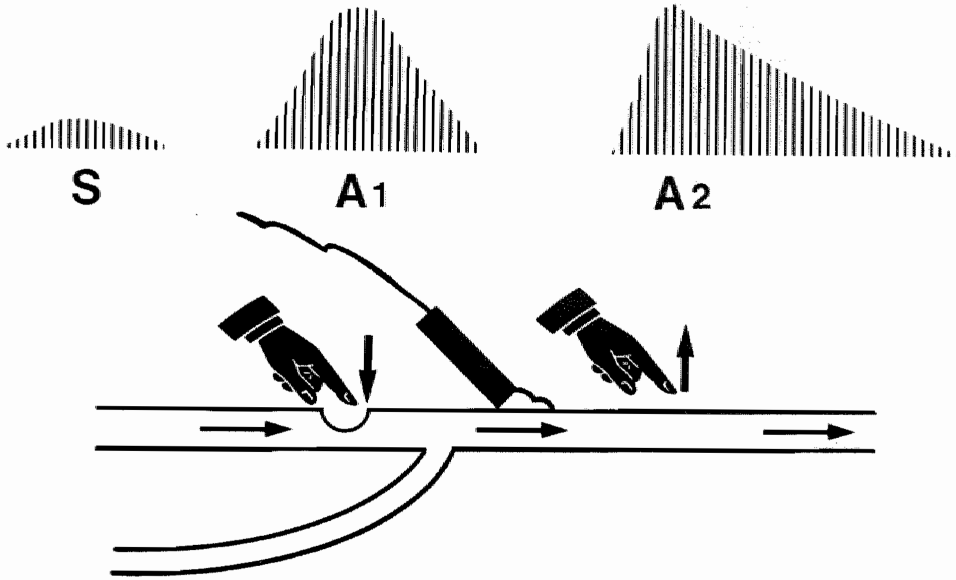
The Doppler velocity was first used for clinical purposes by Johnson [131], who reported that fetal heart action could be detected with Doppler ultrasound as early as 8-10 weeks after conception. In 1966 Strandness reported the use of Doppler ultrasound in arterial disease [243].
Reference to the distinct signal elicited by venous bloodflow was made by Satomura [219] and later by Rushmer [213, 214, 238]. It was again Strandness who, in 1967, reported the alterations in the venous Doppler signal in 17 patients with various venous disorders [244].

3.4.4 Characteristics of venous flow

The apparent differences between arterial and venous bloodflow result in the different properties of the arterial and venous Doppler signals. Heart rate and stroke volume can be considered to be constant during an examination. Apart from the position of the Doppler probe, the arterial signal is only determined by the extent of arterial stenosis when present, and by the peripheral resistance. The same signal is available for examination with each heart beat. Increasing stenoses cause changes in the arterial Doppler signal according to a constant pattern [258].
Venous return is under the influence of heart action, respiration and posture of the patient. The effect of the cardiac cycle can be readily observed from the jugular vein. Collapse of the vein occurs on contraction of the ventricle and on opening of the tricuspid valve [276]. The peripheral conduction of these pressure waves depends on the degree of distension of the central veins. In the upper extremity and the jugular vein, a pulsatile pattern is a normal finding which with Doppler ultrasound can be detected as far down as the dorsum of the hand [189]. In the lower extremity, a pulsatile signal has been observed in congestive heart failure, tricuspid insufficiency and pulmonary hypertension [11, 251, 252], but may be present over the femoral vein in healthy subjects [252]. Influence of respiration is superimposed on the cardiac cycle. There is again a difference between the upper and lower extremity. In the upper extremity venous flow is increased during inspiration, due to the negative intra-thoracic pressure [29, 183]. Conversely, venous flow in the lower extremities is interrupted during inspiration, due to an increase in intra-abdominal pressure [29, 183]. Contraction of the diaphragm could, possibly, have the same influence [83, 190]. This inspiratory decrease in venous flow has been confirmed by electromagnetical flowmetry [183]. Occasionally a predominantly thoracic respiration is performed, such as after laparotomy or in respiratory distress. In these patients venous flow measured over the femoral vein is increased during inspiration [251, 183].

3.4.5 Distinction of venous Doppler signals

The Doppler sound resulting from the natural fluctuations in venous blood flow is referred to as the spontaneous or "S" sound. This S-sound is often described as resembling a windstorm [11, 63, 228], but comparison to the wind blowing through the trees [113, 214] seems more appropriate. The possibility of interfering with the spontaneous signal by manual compression has been appreciated by various authors [214, 244]. It was Sigel [228], who suggested the current classification



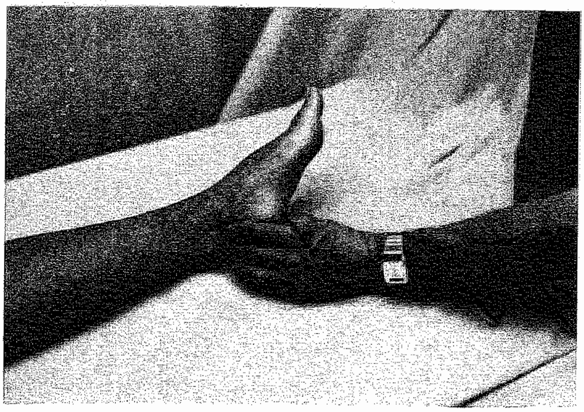
3.4:1

The normal venous Doppler signal: Distinction is made between the spontaneous (S), and the augmented compression (A1) and decompression (A2) sounds.

of these augmented or "A" signals. It seems most simple to refer to the compression A-sound when the squeeze is applied distal to the Doppler probe. According to the sequence of events this would be the first or A1-sound. The second (A2) or decompression sound is heard when pressure proximal to the Doppler probe is released. Both A-sounds are present in the normal situation and their absence is associated with DVT. These different Doppler signals are reflected graphically in figure 3.4:1.
In case of valvular incompetence, a retrograde bloodflow can be elicited [8, 29, 228] which could be referred to as the third A-sound. Thus, Doppler ultrasound can be used to document valvular incompetence as a result of DVT [227, 249]. Other applications include the localisation of incompetent perforating veins [184], congenital malformations [259], and arteriovenous fistulas [29, 244].

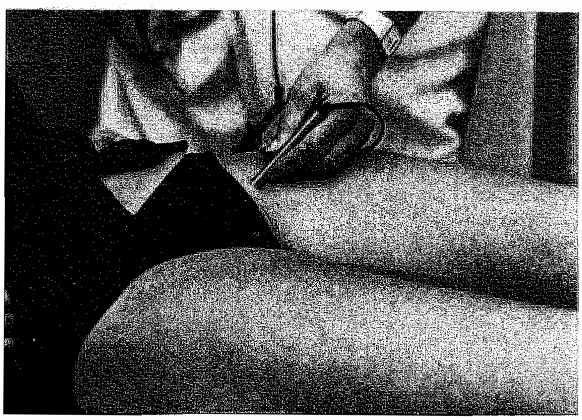
3.4.6 Processing of the Doppler signal

In both arterial and venous disease the Doppler signal can be recorded by means of a zero crossing detector (ZCD). The wide range of detected sound frequencies is converted into a single analogue voltage, which can be displayed on an oscilloscope or strip tract recorder [228, 248]. Spectral analysis provides the total range of Doppler shift signals in relation to the intensity of the signal. Reports on its application in venous disease are limited [230, 244, 250, 266].
However, the most accurate processing of the venous Doppler signal is provided by the sophisticated system in the cochlear nucleï [11, 244].



3.4:2

Examination of the posterior tibial vein behind the medial malleolus. When satisfactory signals are not obtained the examination should be repeated with the leg slightly in flection and exorotation, without pressure of the calf muscles on the examination couch.



3.4:3

Examination of the common femoral vein, medial to the adjacent artery.

3.4:4

Examination of the popliteal vein. A pillow under the feet is essential in order to flex the limb at the knee joint.

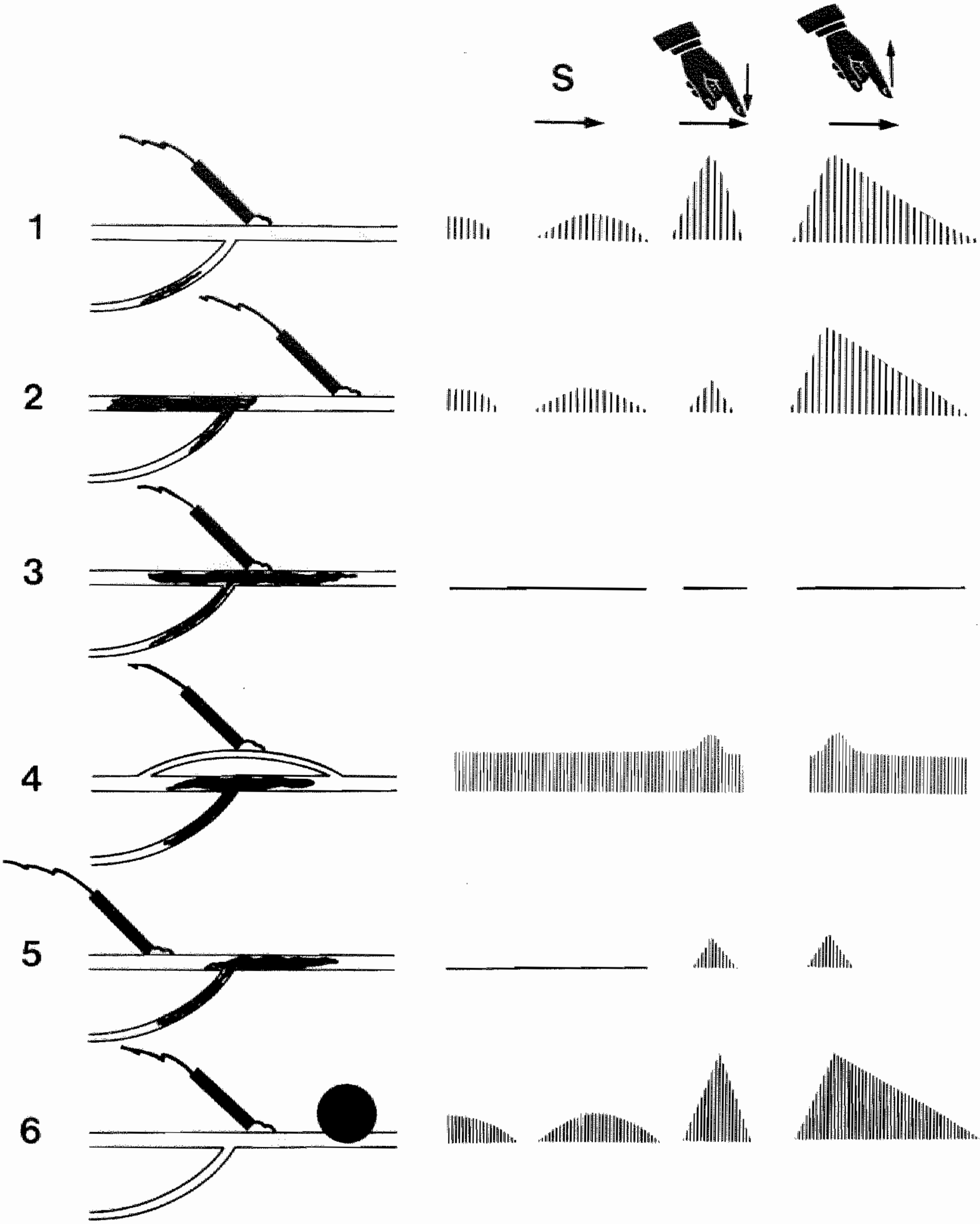
3.4.7 Performance of a venous Doppler examination

A routine examination is performed with the patient or test subject supine in bed or on the examination couch. A cold environment should be avoided. The patient has to lie relaxed with the head and trunk supported by a pillow, to enhance venous pooling in the legs [11,63,230]. The anxious patient should be reassured that he will not be hurt. The examiner too should be at leisure. A sitting position can be of help for this purpose. Acoustical gel is applied to the skin to enhance transmission of the sound beam. The Doppler probe is held at approximately 30-45 degrees to the skin. Pressure exerted by the Doppler probe on the skin should be avoided [30,251]. Each vein can easily be located by looking for the arterial signal first and thereupon shifting the Doppler probe slightly till the concurrent venous signal is heard [71,250,251]. The true phlebologue will use the reverse method to detect the artery. Some authors limit the examination to the common femoral vein (CFV), paying attention to the spontaneous signal and the influence of distal compression [31,73,113,289]. A special calf squeezer was applied by Evans [71,73] in order to provide a predetermined standard pressure of 90 mmHg in all cases. It is expedient however, to perform a complete examination at all levels of the leg [9,245,250,251] and to compare the signals with those of the contralateral leg [247,252,289].

3.4.7.1 Examination of the posterior tibial vein
The posterior tibial vein (PTV) behind the inner malleolus and the concurrent artery is examined first (fig 3.4:2). Attention is directed to the spontaneous (S) signal. This signal can be enhanced by slight flexion and exorotation of the limb [11,30,251]. If no S-sound is heard, the position of the probe should be checked by gently squeezing the foot, which almost invariable causes some augmented signal when the probe is in the proper position. When the S-sound remains absent with the probe in proper position, it can sometimes be evoked by a Valsalva manoeuvre. Subsequently, the compression (A1) and the decompression (A2) signal are evoked by slight pressure on the sole of the foot and by relieving a slight pressure on the calf muscles. Whenever these sounds are not entirely normal, the saphenous vein should be examined for the presence of the harsh continuous sound of collateral flow.

3.4.7.2 Examination of the common femoral vein
The common femoral vein (CFV) is easily located in the inguinal fold, medial to the artery (fig.3.4:3). In the obese, assistance may be required to lift the protruding skin folds. The S-sound and its reaction to respiration are noted. The normal S-sound will be completely interrupted by inspiration.
Augmented signals are elicited by compression of the calf or dorsiflexion of the foot (A dist.) and by compression of the upper thigh (A prox.). A decompression signal can be elicited by compression of the lower abdominal quadrants. This manoeuvre however does not add any information to the flow pattern on inspiration.

3.4.7.3 Examination of the popliteal vein
For examination of the popliteal vein (PV), the patient is preferentially examined in a prone position with the feet supported by a small pillow [63,228,245,251]. Slight flexion of the knee joint is essential (fig 3.4:4). Because of the course of the PV, the Doppler probe can be held at approximate right angles to the skin.
In the severely obese, the pregnant and the lethargic patient this position can not always be achieved. Alternatively, the patient can be requested to turn sideways or the legs can merely be flexed and exorotated [11]. A reliable examination of the PV is not always possible in this position. As whith the examination of the other veins, the S-sound is looked for first. The compression sound is evoked by slight pressure of the calf muscles. The decompression signal can be difficult to elicit. Rather firm compression has to be applied over the medio dorsal side of the thigh, which makes it a less reliable feature.



3.4:5

Influence of various circumstances on the venous Doppler signal. On the left different relations between the thrombus and the Doppler probe are presented schematically, with the corresponding spontaneous and augmented venous Doppler signals on the right.

3.4.8 Criteria of normal and pathological Doppler signals

3.4.8.1 The normal Doppler signal

An important feature of the normal S-sound is the complete interruption during inspiration [30,244,251]. The presence at all levels of the normal limb has not been generally observed. There is general agreement that an S-sound should be heard over the common femoral vein in all patients.

Sigel [230] states that it is heard over the popliteal vein in only half the cases and is usually not heard over the posterior tibial vein. Conversely Sumner [251] and Barnes [11] report that an S-sound should always be heard over the CFV as well as over the PV, and that with sufficient attention it is heard in most cases (87-95%) over the PTV as well.

Absence of the S-sound over the PTV can be due to venoconstriction caused by a cold environment, anxiety or pain [11,252].

Whenever a vein is patent, compression and decompression sounds can be evoked at a short distance from the Doppler probe with only slight pressure. Propagation distally is normally interrupted by competent valves. Proximal propagation is reported to be detectable by ultrasound at a distance of more than 1 meter [230]. An empty and collapsed vein, however, will fail to conduct the pressure wave. According to Sumner [251] a squeeze in the calf does not invariably cause an A-sound over the CFV.

3.4.8.2 Influence of thrombosis on the venous Doppler signal

Unfortunately, DVT does not alter the Doppler signal according to a constant pattern. Alterations of the spontaneous and augmented Doppler signals as they are to be expected in different situations are presented in fig 3.4:5.

1. In a patient with a non-obstructing thrombus, or sufficient collaterals, undisturbed Doppler signals may be observed [19,40,169,230,290]. Similarly a thrombus in a tributary vein, such as the peroneal, anterior tibial, soleal, deep femoral and internal iliac veins, will not alter venous flow and will remain undetected by non-invasive examination [19,30,146,230].
2. Proximal to an occlusion, a normal spontaneous and decompression sound will be obtained. When compression is applied distal to the occlusion, augmentation of flow will usually not occur [9,228]. In a case with sufficient collaterals, however, a diminished but sometimes confusing A-sound will be observed [230].
3. Over an occluded venous segment no Doppler signal is present at all [245,251].
4. When a major vein is occluded, flow through superficial collateral veins is increased. The collateral flow causes a continuous high pitched Doppler signal [11,230,251]. These collaterals can be recognised as such, because they are easily compressed by the Doppler probe and usually fail to follow a straight course. This collateral sound can also be observed over the saphenous vein when major DVT is present [11,30,251].

Deceivingly, a continuous sound can be present in a hyperaemic state such as in reactive hyperaemia [29] or inflammation [9].

5. Distal to an occlusion the spontaneous sound is absent, or when present, lacks the influence of inspiration [9,30,244,245,250,289]. The augmented sounds are usually present in this situation, and are even louder than usual because of venous congestion. These augmented signals are usually dull sounding because of the impeded flow velocity. The decompression sound, obtained from the PTV, has a characteristic abrupt ending [11,30,146,251], while it slowly fades away in the normal limb.
6. In the case of external compression without complete obstruction of the vein, the Doppler signal will be unusually loud, but otherwise unaltered.

Some authors [30,63,251] rely mainly on the observed S-sound. Others [73,228] ascribe a greater accuracy to the augmented compression sound. The diminished decompression sound obtained from the PTV is regarded as the best indication of major DVT by Barnes [11]. Because of the gradual differences between normal and DVT, comparison with the contralateral leg is always important in the judgement of the venous Doppler signal [28,245,252,289].
In sum, the following criteria fit with either a normal venous system or DVT:

Normal

Spontaneous sound present
Phasicity with respiration
Augmentation with distal compression and proximal decompression
Lack of retrograde flow
(non pulsatile) [11,30]

DVT

Absence of S-sound over major veins
Continuous S-sound
Increased superficial flow
Absent or diminished augmented signals
Abrupt ending of augmented sounds [9,30,251]

Recognized causes of misinterpretation of the venous Doppler signal are:

Use of an inappropriate emission frequency
Incorrect positioning of the patient
Failure to appreciate the influence of edema, hematoma or subcataneous fat tissue
Increased venous flow due to inflammation
Influence of an arterio-venous fistula
Tense muscles
Congestive heart failure
Excessive pressure on transducer
External compression
Non occlusive thrombi

The one common denominator is: inexperience [19,30,146,251].

3.4.9 Results of venous Doppler examination

The first reports of pathological venous Doppler sounds were merely descriptive [29, 244].
Shortly thereafter results were published on the first series of patients investigated with both Doppler ultrasound and venography [72, 228]. The accuracy of this method of investigation has since been confirmed by many others.
For an appropriate evaluation of the venous Doppler examination, those studies have been selected in which consecutive patients, all with a clinical diagnosis of DVT, were examined with both Doppler ultrasound and venography (table 3.4:I). Because of the difference in sensitivity for calf vein and proximal thrombosis, these conditions should be mentioned separately.
There appears to be a large variation in the accuracy reported by different authors, probably due to the subjective nature of the test.
For the collected series of 1348 patients, the specificity amounts to 702/850 (82.5%). The sensitivity for CVT is 78/167 (46.7%), while it is 266/331 (80.3%) for proximal thrombosis. Of course, proximal extension of the thrombus does not indicate whether occlusion has taken place, and non-occlusive thrombi are likely to escape detection. The negative predictive value of a normal test result is 702/856 (82%) for DVT not to be present, while the positive predictive value of an abnormal test result for DVT to be present is 344/492 (69.9%).
When surgical patients are screened during the postoperative period, silent calf vein thrombosis as detected by the 125 I fibrogen uptake test generally remains unobserved by Doppler examination [31, 142, 172], although favourable results have been reported [164].

Table 3.4:I
Results of Doppler ultrasound examination in consecutive symptomatic patients, compared with the result of venography. The number of true negative results indicates the specificity of the test, whilst the sensitivity is given by the number of true positive results.
The predictive value indicates the probability that DVT is not present in those patients with a normal venous Doppler signal, and the probability that DVT is present in those patients with a pathological Doppler signal.

Author	Year	Number of examined limbs	Normal	Spec.%	CVT	Sens.%	Prox DVT	Sens.%	Overall DVT	Sens%	Predictive value TN/TN+FN (Normal)	Predictive value TP/TP+FP (Pathologic)
Holmes	1973	71	46/49	94	0/5	0	17/17	100	17/22	77	46/51 = 90%	17/20 = 85%
Barnes	1976	55x clin. CVT	29/37	78	17/18	94			17/18	94	29/30 = 96%	17/25 = 68%
Meadway	1975	120	55/76	72	3/10	30	29/34	85	32/44	72	55/67 = 82%	32/53 = 60%
Flanigan	1978	169	94/98	96	4/17	23	35/54	65	39/71	55	94/126 = 75%	39/43 = 91%
Sumner	1979	192	104/121	86	32/35	91	34/36	94	66/71	93	104/109 = 95%	66/83 = 80%
Muller-Brand	1979	137	45/71	64	3/17	18	35/49	71	38/66	58	45/73 = 62%	38/64 = 59%
Holden	1981	138	87/96	91	3/16	19	21/26	81	24/42	57	87/105 = 83%	24/33 = 73%
Bounameaux	1983	87	21/34	62	5/13	38	33/40	82	38/53	72	21/36 = 58%	38/51 = 74%
Bendick	1983	140	85/94	90	3/16	19	22/30	73	25/46	54	85/106 = 80%	25/34 = 73%
Zielinsky	1983	189	117/153	76	6/15	40	20/21	95	26/36	72	117/127 = 92%	26/62 = 42%
Sandler	1984	50	19/21	90	2/5	40	20/24	83	22/29	75	19/26 = 73%	22/24 = 92%
Total		1348	702/850	82%	78/167	46%	266/331	80%	344/498	69%	702/856=82%	344/492=70%

3.4.10 Conclusions

Because Doppler ultrasound is simple and safe in performance, it should be regarded as a valuable method to evaluate the patient with suspected DVT.

Because of the large range in the reported results, there is a need for strictly defined criteria for interpretation of the results. When one is aware that CVT usually will not be detected, therapeutic decisions are justified. The fact that experience is required should not be a reason to abandon the method, but rather an incentive to create well organised courses for instruction.

3.5 Measurement of venous outflow: Kenoseography

3.5.1 Nomenclature

The recording of volume changes in health and disease has always been designated as "plethysmography". This was supposed to be a correct term for the recording (graphein) of an increase in volume (plethysmos).
The first "plethysmographyic" recordings are ascribed to Glisson (1622) and Swammerdam (1737) [128]. Since Glisson and Swammerdam did, in fact, record the volume of muscle to be constant on contraction, their measurement should probably have been referred to as "isography". This is, however, merely a historical point. Venous outflow measurement is currently a common procedure in the diagnosis of deep venous thrombosis. Outflow measurement is related to the recording of volume decrease of a limb. For this reason another indication than "plethysmography" is needed and it seems that a suitable alternative can be taken from ancient Greek medical literature.
Hippocrates (5th century B.C.) [108] distinguished between diseases caused by a surplus of liquids and those caused by a shortage of them. He used the term "kenosis" (=emptying evacuation) in a polar opposition to "plêsmône" (=being filled, repletion, statiety). More in particular, he uses "kenosis" for "fluid depletion" such as caused by vomiting, perspiration, sexual intercourse and the like. Galenus (2nd century A.D.) [87] took "kenosis" from his great predecessor and used it for the same purpose. In one particular passage he observes that this term is particularly apt (akribestatê) for the withdrawal of blood from the body by phlebotomy.
This last statement by Galenus comes closest to describing what is done in venous occlusion "plethysmography", when the occlusion cuff is deflated and the pooled blood is flowing back into the inferior vena cava. Therefore it seems appropiate to coin the term "kenoseography" for the examination which measures venous outflow from a limb [270].

3.5.2 Historical notes

Plethysmographic measurement of arterial bloodflow was first described by Brodie in 1905 [37]. Arterial inflow was assumed to be equal to the volume increase of a kidney, in the first moments after clamping of the renal vein. This principle is nowadays generally known as venous occlusion plethysmography (VOP).
Brodie suggested applying the method on a limb by compressing the veins with a ligature. At present this is the most common application of this examination. The ligature has, however, been replaced by a compression cuff.
In this manuscript Brodie also remarks on the venous outflow.
Other preliminary notes on venous outflow were made by Lewis in 1925 [155] and Nyboer in 1950 [191]. The latter recorded a decrease in volume of 14.5 ml by elevation of the arm of a normal subject.

3.5.3 Instrumentation

Initially recordings were made by measuring volume displacement of the medium which surrounds the subject of study. The organ to be studied is placed in a rigid chamber, filled with either water or air. To prevent leakage, the limb is enclosed by a diaphragm. In a small bore recording tube or "chimney" the volume of displaced fluid can be measured. Displacement of air can be transferred directly to a sensor or writing device [253]. The main disadvantage of water plethysmography is that its performance is rather cumbersome, which makes it less suitable for clinical application. Furthermore, registrations could be influenced by a gartering effect from the diaphragm and by the hydrostatic pressure.
Air-plethysmography by means of cuffs, inflated to enclose the limb snugly, is used to record

arterial pulse waves quantitatively (pulse volume recorder) [43, 207]. In venous disease the method is modified to record the volume changes resulting from respiratory action (Rheophlebography) [54].

Currently two methods to determine volume changes in an indirect way are most commonly used: strain-gauge Kenoseography (SKG) and Impedance Kenoseography (IKG).

3.5.4 Strain-gauge Kenoseography

Strain gauges, introduced by Whitney in 1949 [283], are used to measure changes in the circumference of the limb. They consist of a silicon tube filled with Mercury or, more recently, an Indium alloy. Their mode of action and application were described more extensively in a following paper [284]. The principle is based on the assumption that the cross section of a limb is approximately circular and that the volume changes occur entirely in the transverse plane of the limb.

Changes in volume ($\pi r^2 L$) are related to changes in circumference ($2\pi r$). For small changes in volume this relation is described by the formula:

$$dV/V = 2dC/C$$

where:
V= volume
C= circumference [253, 284]

Stretching of the strain gauge causes a change in electrical resistance, which is proportional to the amount of stretching [283]. As a consequence volume changes are related to changes in resistance according to the formula:

$$dV/V = dR/R$$

where:
V= volume
R= electrical resistance of the strain-gauge

The strain-gauge is capable of reproducing a stimulus, changing with a frequency of 100 Hz [197]. Calibration was at first done mechanically by stretching the gauge over a known distance. Later a method for electrical calibration was described to simplify the procedure [34, 99]. For this purpose the strain gauge is connected to a Wheatstone bridge during measurements.

Gauge length usually does not fit the limb circumference precisely. To overcome this gap, a non-distensible part is present, of which the length can be varied to fit the gap. The gauge itself can be supported with sliding links. If the gauge does not fit the limb entirely, volume changes are corrected as follows:

$$dV/V = 1/p \times dR/R$$

where p is the ratio of the distensible part and total length of the gauge surrounding the limb [145].

Since calf circumference does not increase uniformly, the non-distending part of the gauge should be placed over the anterior (non-distending) part of the lower limb [145].

3.5.5 Impedance Kenoseography

With Impedance Kenoseography (IKG) the limb is considered to be a cylindrical conductor of which the resistance is:

$$R = \frac{\varrho L}{\pi r^2}$$

where:
ϱ = *resistivity of the medium*
L = *length*
πr^2 = *cross section*

This equation can also be written as:

$$R = \frac{\varrho L^2}{Volume}$$

Resistance is therefore reversely proportional to the volume of the limb. For small changes in volume the following relation can be assumed:

$dR/R = -dV/V$ [191, 192, 253]

To perform an IKG examination, two electrodes are placed circumferentially proximal and distal to the part from which changes are to be measured. Through these electrodes a current of 1 mA and a frequency of 30-50 KHz is applied, which cannot stimulate the heart [277, 278]. Voltage changes are recorded by two other electrodes which are placed in between the former two [179, 191, 282].
The distance between the electrodes varies from 12 to 18 cm but small changes do not appear to be critical [60].

3.5.6 Choice of recording equipment

Comparison of values of arterial inflow obtained by water plethysmography and electromagnetic flowmetry have been shown to be in agreement [208]. Simultaneous measurements with water-kenoseography and SKG [57, 80, 284] or SKG and IKG [13, 280] resulted in identical recordings. Strandness [246] states that the choice of one or another registration method is arbitrary. The results will be identical.
Differences between IKG and the other methods have only been reported in the case of fast changes in bloodflow, in the sense that IKG lags behind [282]. This is also apparent in the peak of the arterial pulse, which is narrow when recorded with strain-gauges and broadens with impedance measurement [130].
With venous outflow measurement the IKG shows a spike on rapid deflation that is lacking in the other methods. Apart from blood volume, impedance changes might be caused by shape and position of red blood cells, which show realignment on sudden increase in flow velocity [130].
Finally, a high content of red blood cells causes relatively greater changes in impedance, when compared to an anaemic state.

3.5.7 Application of Volume measurement

Different methods of plethysmography have been employed in physiological experiments. Recording the bloodflow to an organ or limb [37] has been extended to the investigation of the influence of temperature [42, 284] and various other stimuli such as alcohol, nicotine and a nerve block on the peripheral circulation.
At present plethysmography is most commonly used in the evaluation of peripheral vascular disease. It can be used to examine arterial disease in different ways. Blood pressure can be measured using a strain gauge to detect the first pulsations on deflation of the pressure cuff [242]. Values obtained in this way approximated the manometry pressure by 5 mm Hg [112].
Amplitude and morphology (dicrotic notch) of the arterial pulse can be evaluated. Arterial flow volume can be measured with the venous occlusion technique, either directly with a water plethysmograph [55], or indirectly with SPG or IPG. With these indirect methods flow is determined by the tangent of the initial part of the plethysmogram after venous outflow has been obstructed.

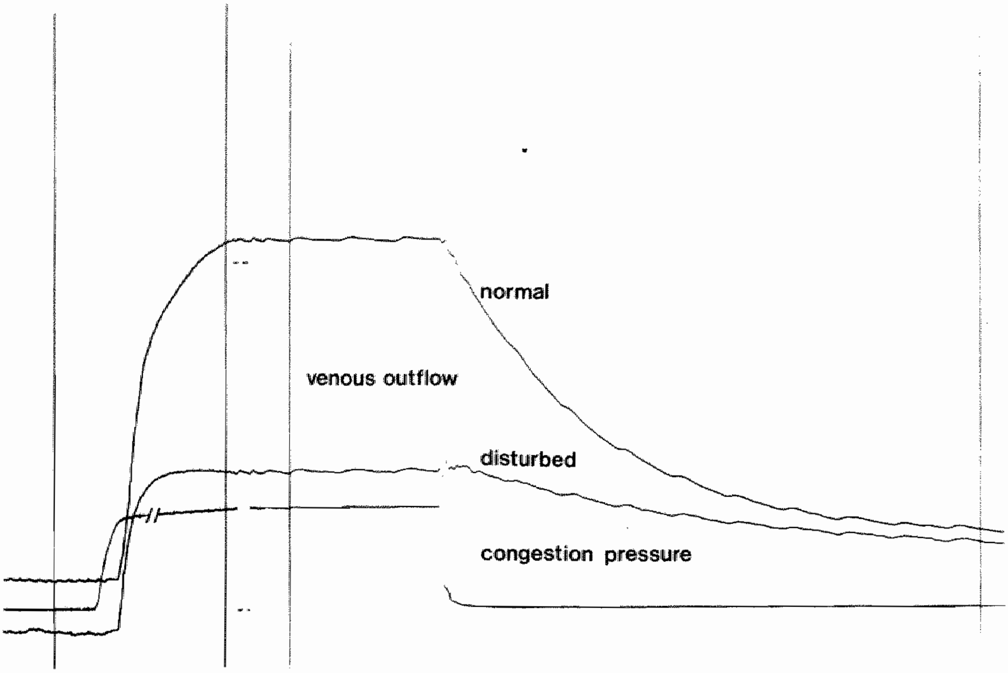
3.5.8 Venous examination

Clinical use of "plethysmography" for venous disease was derived almost accidently from arterial examinations. While observing the arterial pulse volume with IPG, Wheeler [277] noted a change of the base line, simultaneous with respiration. Closer study of this phenomenon showed that a deep breath results in an impedance change of more than 0.2% in healthy subjects.
In the case of venous obstruction this response did not occur. A drawback is that cooperation of the patient is required, in that he has to be able to hold his breath for 5 seconds after deep inspiration. Because of this problem most authors have converted to the use of venous occlusion Kenoseography (VOK), for investigation of venous disease [61, 279]. While performing venous occlusion plethysmography for arterial disease, Dahn [56] had noted that in some patients the usual fast volume recovery after cuff deflation was remarkably retarded. In these patients the venogram invariably showed signs of thrombosis.

These observations have been confirmed by examination of patients with venographically registered DVT. In 9 patients a venous evacuation rate of averagely 160 ml/min was found, compared to 760 ml/min for the contralateral leg [56].

3.5.9 Performance of venous occlusion Kenoseography

Venous outflow measurement is commonly performed with the patient lying on an examination-couch with the limbs elevated to enhance venous outflow. A compression cuff is placed around the mid thigh and inflated to a preset level well below the arterial pressure. A gradual increase in volume will occur distal to the congestion cuff (congestion phase) until the venous pressure equals the cuff pressure. At this moment a plateau phase is reached at which the cuff is deflated resulting in the venous outflow phase (fig 3.5:1). With increasing cuff pressure, a true plateau phase will not occur due to edema formation [231], but this can generally be distinguished from venous filling.
In a limb with DVT both volume increase (Venous Capacity= VC) and outflow velocity are markedly impaired (fig 3.5:1).The VC will be smaller because a part of the venous lumen is already occupied by thrombi. Pre-existent venous congestion and increased tissue pressure will further limit pooling of venous blood [56]. After release of the congestion pressure, venous outflow (VO) will be diminished due to the increase in flow resistance by the thrombus.



3.5:1

A normal and pathological Kenoseogram. The time scale is presented on the abscissa, the changes in volume on the ordinate. The lower tracing represents the congestion pressure in the cuff. During the congestion phase a gradual increase in volume occurs, which is considerably less in the thrombotic limb. After release of the congestion pressure, venous outflow ensues, which is markedly impeded in the thrombotic limb.

3.5.10 Venous Outflow Determination

Venous outflow can be approached mathematically. Volume flow through a rigid tube is governed by Poiseuilles law:

$$Q = \frac{K \times P \times di^4}{L} \qquad (1)$$

where:

Q = volume flow
P = pressure drop along the tube
di = inside diameter
L = tube length
K = a constant depending on fluid viscosity

According to Strandness [246] the formula corresponds with Ohms law:

$$I = \frac{V}{R} \qquad (2)$$

where:
I = *electrical current*
V = *voltage*
R = *resistance*

Poiseuilles law could be rewritten as follows:

$$Q = \frac{P}{R} \qquad (3)$$

where:
Q = *volume flow*
P = *pressure difference between calf veins and the vena cava inferior*
R = *venous resistance*

With regard to venous outflow after release of a pressure cuff, the flow will decrease with time, proportional to the exponential drop in venous pressure distal to the occlusion cuff [246]. The rate at which the pressure declines depends on the resistance of the proximal venous system (R), as well as on the elasticity (E) of the venous wall [246, 254]. With these data, venous flow at any time after cuff release is determined as follows:

$$Qt = \frac{E}{R} \times Vo \times e^{-(E/R)t} \qquad (4)$$

where:
Q = *flow*
E = *P/V (venous pressure/venous volume)*
Vo = *maximal extent of venous capacity*
R = *venous resistance*
t = *time after cuff release in seconds*

At the moment of cuff release outflow is maximal and can be written as:

$$Qo = MVO = \frac{E}{R} \times Vo = \frac{Po}{R} \qquad (5)$$

From this formula several statements can be derived, reflecting on the interpretation of Kenoseography,
- Venous outflow is reciprocal to venous resistance (while resistance increases in case of DVT)
- Venous outflow is proportional to the venous capacity (VC)
- Venous outflow is proportional to P and therefore dependant on the cuff pressure

Formula 5 can be rearranged as follows:

$$R = \frac{E \times VC}{MVO} \qquad (6)$$

From this formula two other statements can be derived :
- Given a certain venous expansion (VC), the greater the venous outflow, the less the resistance and thus the smaller the probability of DVT.
- Given a certain outflow (MVO), the greater the venous volume (VC), the greater the resistance and, therefore, the greater the probability of DVT (6).

These statements explain the relation between venous capacity and venous outflow, which is used by many authors to increase the accuracy of interpretation of the Kenoseogram [20, 27, 85, 118, 279]. However, the validity of these two statements is limited by the proportional relation between MVO and VC.

3.5.11 Results of kenoseography

Despite refinements, kenoseography remains insensitive to calf vein thrombosis [118, 282] and non-obstructive thrombosis in the proximal veins [118].
Moreover, kenoseography does not measure thrombosis but only volume changes which are at best a reflection of venous outflow.
False positive results are caused by extrinsic venous compression by a tumour in the pelvis, a gravid uterus, for instance. Other possible causes are enlarged lymphe nodes, a Bakers cyst or hematoma [20, 101, 279].
Arterial disease is also reported to be associated with a decrease in VC and VO [27]. Bilateral reduction in venous outflow can be observed in patients with an increased muscle tone, vasoconstriction and circulatory failure [79].

When Kenoseography is to be used in the management of a patient with suspected DVT, we have to know the predictive values of normal and abnormal test results.
As for the evaluation of Doppler ultrasound, these predictive values should be derived from studies in consecutive symptomatic patients who have been examined with both kenoseography and venography.
Because of the low sensitivity for calf vein thrombosis these patients should be mentioned separately.
Results of studies responding to these criteria are presented in table 3.5:I and 3.5:II. For the collected series the results are as follows:

Table 3.5:I

Results of strain gauge Kenoseography in consecutive, symptomatic patients, compared with the result of venography. The numer of true negative results indicates the specificity of the test, whilst the sensitivity is given by the number of true positive results. The predictive value indicates the probability of DVT not to be present in patients with a normal venous outflow, and the probability of DVT to be present in patients with a disturbed venous outflow.

Author	Year	Number of examinations	Normal	Spec.%	CVT	Sens.%	Prox DVT	Sens.%	Overall DVT	Sens%	Predictive value TN/TN+FN	Predictive value TP/TP+FP
Hallböök	1971	106	70/70	100	0/5	0	31/31	100	31/36	86	70/70 = 93%	31/31 = 100%
Barnes	1972	90	33/40	82	0/7	0	41/43	95	41/50	82	33/42 = 79%	41/48 = 85%
Barnes	1977	387	259/318	81	25/38	66	28/31	90	53/69	77	259/275 = 94%	53/112 = 47%
Boccalon	1981	69	28/28	100	13/15	87	26/26	100	39/41	95	28/30 = 93%	39/39 = 100%
Bounameaux	1983	83	21/34 (?)	63	7/12	58	35/37	95	42/49	86	22/29 = 76%	42/54 = 78%
Abu Rahma	1983	106	63/80	78	0/1	0	25/25	100	25/26	96	63/64 = 98%	25/42 = 59%
Franzeck	1983	33			3/9	33	20/24	83	23/33	70	?	?
Pini	1984	269	132/141	94	11/19	60	105/109	97	116/128	91	132/144 = 92%	116/125 = 95%
Total		1143	606/711	85	59/106	56	311/326	95	370/432	86	606/668 = 91%	370/475 = 78%

Table 3.5:II

Results of Impedance Kenoseography in consecutive, symptomatic patients, compared with the result of venography. The numer of true negative results indicates the specificity of the test, whilst the sensitivity is given by the number of true positive results. The predictive value indicates the probability of DVT not to be present in patients with a normal venous outflow, and the probability of DVT to be present in patients with a disturbed venous outflow.

Author	Year	Number of examinations	Normal	Spec.%	CVT	Sens.%	Prox DVT	Sens.%	Overall	Sens%	Predictive value TN/TN+FN	Predictive value TP/TP+FP
Johnston	1974	64	35/38	92	3/12	25	14/144	100	17/26	65	35/44 = 79%	17/20 = 85%
Wheeler	1975	168	106/108	98	3/19	16	40/41	98	43/60	72	106/123 = 86%	43/45 = 96%
Richards	1976	150	78/90	87	9/23	39	30/37	81	39/60	65	78/99 = 79%	39/51 = 76%
Hull	1976	618	386/397	97	15/88	17	124/133	93	139/221	63	386/468 = 82%	139/150 = 93%
Hull	1977	200	108/114	95	5/26	19	59/60	98	64/86	74	108/130 = 83%	64/70 = 95%
Benedict	1977	267	154/161	96	6/27	22	77/79	97	83/106	78	154/177 = 87%	83/90 = 92%
Flanigan	1978	169	93/98	95	12/17	71	52/54	96	64/71	90	93/102 = 91%	64/69 = 95%
Toy	1978	28	9/9	100	1/3	33	15/16	94	16/19	87	9/12 = 75%	17/17 = 100%
Hull	1981	274	157/169	98	5/36	14	74/78	95	79/114	69	157/190 = 83%	81/84 = 96%
Wheeler	1982	342	191/208	92	21/44	47	88/90	98	109/134	81	191/216 = 88%	109/126 = 87%
Peters	1983	185	115/124	92	15/22	68	36/39	92	51/61	84	115/125 = 92%	51/60 = 85%
Satiani	1985	176 (21 border line results)	76/100	76	9/19	47	49/57	86	58/76	76	76/94 = 81%	58/82 = 71%
Total		2641	1508/1607	94	104/336	31	658/698	94	762/1034	74	1508/1780 = 85%	762/861 = 89%

	Strain-gauge Kenoseography	Impedance Kenoseography
Number of examinations	1143	2641
Correctly identified patients without DVT (specificity)	606/711 (85%)	1508/1607 (94%)
Correctly identified CVT (sensitivity)	59/106 (56%)	104/336 (31%)
Correctly identified PT (sensitivity)	311/326 (95%)	658/698 (94%)
Overall sensitivity	370/432 (86%)	762/1034 (74%)
Predictive value normal result	606/668 (91%)	1508/1780 (85%)
Predictive value abnormal result	370/475 (78%)	762/861 (89%)
Overall accuracy	976/1143 (85.3%)	2270/2641 (85.9%)

Deep venous thrombosis was present in 432/1143 (38%) and 1034/2641 (39%) of the patients, CVT being encountered slightly more often in the IKG series; 9.3 and 12.7% respectively.The results in both series appear to be almost identical. Differences could be ascribed to the examined populations, and to different ways of determining the test results. In the SKG series venous outflow was generally obtained, whilst the Hull Nomogram was applied in most of the IKG studies.
In the SKG series a better sensitivity is obtained, mainly due to the results in patients with CVT (86 and 74% respectively). This high sensitivity comes at the expense of specificity, which is better in the IKG series (85 and 94% respectively). The sensitivity for proximal thrombosis (95 and 94%) and the overall accuracy (85%) are equal in both series.

3.5.12 Conclusions

When correctly performed, kenoseography supplies a more or less objective figure for the venous outflow, which can be compared with reference values as well as with previous and future examinations. Calf vein thrombosis is known to be overlooked by this method, but it has been shown to be safe to withhold anticoagulants in patients with a normal test result [13, 127, 281]. In patients with an abnormal recording, it should be borne in mind that kenoseography only reflects impeded venous outflow, and not the cause of outflow obstruction.
With these restrictions, kenoseography is a valuable acquisition in the management of patients with suspected DVT.

IV Basic study on the venous Doppler signal and venous outflow measurement.

4.1 Quantitative analysis of the normal and pathological Venous Doppler signal

4.1.1 Introduction

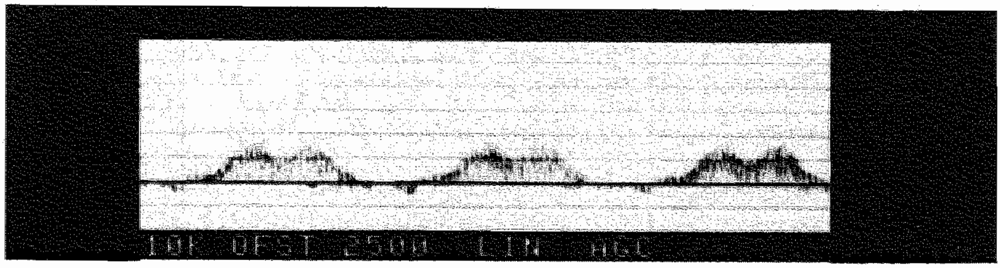
In order to obtain a better understanding of the venous Doppler signal, spectral analysis was performed in 15 young and healthy test subjects and 29 patients with a clinical diagnosis of DVT. In the test subjects, spontaneous and augmented signals were recorded at three levels. Of the 29 patients, 11 had a normal venous system on venograhy, 5 had calf vein thrombosis (CVT) and 10 had proximal extending thrombosis with calf vein involvement (PT). In 3 patients iliac vein occlusion was present with patent femoral and crural veins. In the patients, attention was directed to the augmented signals at the level of the PTV.
For this purpose a bidirectional Doppler apparatus with an emission frequency of 10 MHz for the superficial (PTV), and 5 MHz for the deep (PV and CFV) veins was used *(Vasculab model D10 Medasonics)*, together with a spectral analyser *(800 Radionics Medical)*. With this device, the Doppler sound is displayed on a fluorscopic screen with the time base on the abscissa and the frequency on the ordinate. The intensity of the visual signal is proportional to the loudnes of the acoustical signal. A spectrum from a chosen point of this signal can be displayed simultaneously, in which the frequency is displayed on the abscisa and the loudness on the ordinate (fig 4.1:1-4).
Thus maximal frequency and duration of the signal could be determined accurately. A statistical account is presented in chapter 5.4.

4.1.2.a The spontaneous signal

In the test subjects a spontaneous signal was present at the level of the PV and CFV in all cases (30 limbs), and in all but 3 cases (3 limbs in 2 subjects) at the level of the PTV. In 11 test subjects in whom the brachial vein (BV) was examined as well, a spontaneous signal was present in all cases. The maximal frequency of the S sound in the lower limb gradually increases from 0.46 KHz at the level of the ankle, to 1.13 KHz in the groin (fig 4.1:1, table 4.1:I). Apparently venous flow is slow, but with a rather constant velocity in the distal veins, while it is more easily interrupted by respiration, with a higher maximal velocity and thus a higher maximal frequency in the more proximal veins.

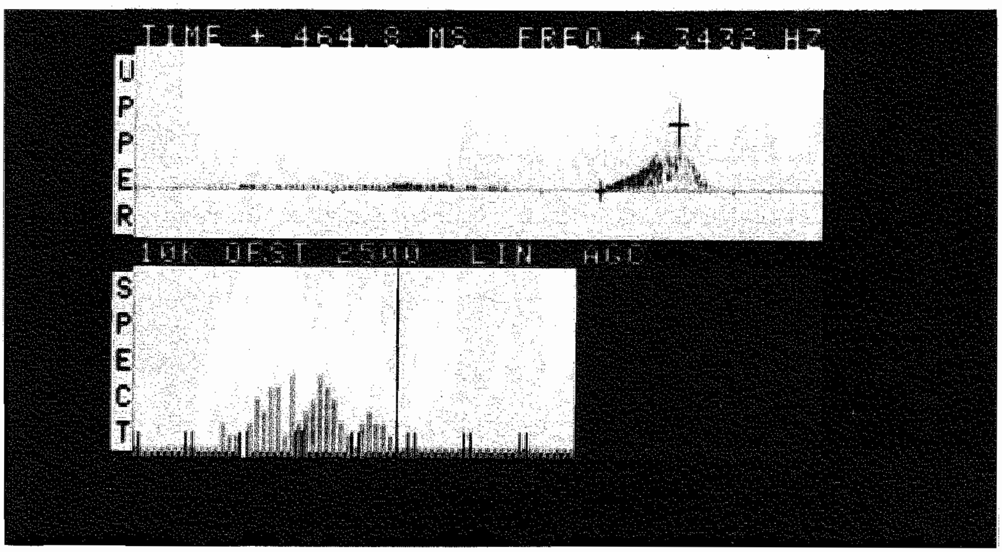
4.1.2.b Respiratory changes

Spontaneous venous flow in the lower extremity decreases on inspiration, as a result of the increased intra abdominal pressure. In the upper extremity, a reverse flow pattern would be expected to occur because of the negative introthoracic pressure during inspiration. In the present study however, flow in the brachial vein decreased on inspiration in 10/22 of the examined arms. Flow increased in 9 and remained constant in 3 cases. The same observation, volume increase on inspiration, was made with strain-gauges. The interruption of venous flow on inspiration could be explained by the entrapment of the subclavian vein in the anterior scalenus triangle.



4.1.:3

Biphasic pattern of the pulsatile venous Doppler signal.



4.1:4

Spontaneous and compression sound obtained from the posterior tibial vein. Note the moderate frequency and loudness of the compression signal.

4.1.2.c Pulsatility of venous blood flow

In the upper extremity a pulsatile pattern was present in 14/22 of the examined arms. Pulsatile flow can be ascribed to the transmission of pressure changes in the superior caval vein, synchronous with the cardiac cycle. This pulsatile pattern is generally thought not to be transmitted to the lower extremity, unless congestive heart failure or tricuspid valve insufficiency is present. In the examined test subjects however, pulsatile flow was observed over the CFV in 5/15 of the subjects (10/30 limbs). These pulsations were synchronous with the arterial signal indicating their cardiac origin, wherease they faded on inspiration, proving the venous nature of the signal (fig 4.1:2). This cardiac induced venous signal shows a biphasic pattern, probably corresponding with the x and y descent of the jugular venous pulse (fig 4.1.:3). Jugular venous pressure is decreased and the corresponding distal venous flow could be increased on ventricular contraction and on opening of the tricuspid valves.

4.1.3.a The compression signal

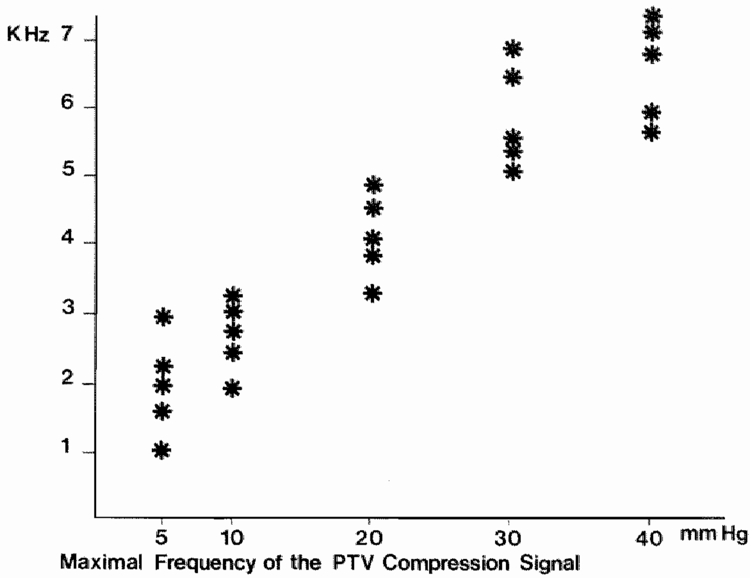
In the test subjects a compression sound was obtained over the PTV and PV in all cases (fig 4.1:4). Whilst examining the CFV, proximal compression over the thigh also resulted in an augmentation of the signal in all cases, but distal compression failed to do so in 3 subjects (6 limbs). The average values of the peak frequencies are displayed in table 4.1:I. The values for the peak frequency obtained from the PTV, PV, and the proximal compression sound obtained from the CFV show a close resemblance, being 2.8 2.4 and 2.5 KHz (SD 0.8-1) respectively. The distal compression sound obtained over the CFV is clearly different from the other compression signals, with an average value of 1.6 KHz (SD 0.9, $p<0.001$).

4.1.3.b Relation between pressure and maximal frequency

The maximal frequency of the compression signal is likely to be related to the exerted pressure. The relation between pressure and maximal frequency was studied in 5 additional test subjects. Similarly to Evans[71,72], a sphygmomanometer cuff was used for pressure application. This cuff was connected to a device capable of producing a predetermined pressure almost instantane-

Table 4.1:I
Average values and standard deviation (SD) of the maximal frequency (KHz) and duration (sec) of the venous Doppler signal obtained from various levels in test subjeccts and patients with a normal venogram, and from patients with calf vein or proximal thrombosis. The S-sound, compression (A_1) and decompression (A_2) sound are mentoined separately.

	No.	PTV				PV				CFV	
										prox.	
		frequency (SD)		duration (SD)		frequency (SD)		duration (SD)		frequency (SD)	
S Sound											
test subjects	10	0.46	(0.21)			0.56	(0.20)			1.13	(0.36)
A_1 sound											
test subjects	10	2.76	(1.08)			2.35	(0.83)			2.47	(0.81)
Normals	11	1.88	(0.65)			1.2	(0.5)				
CVT	5	1.95	(1.62)								
PT	10	1.02	(0.50)								
A_2 sound											
test subjects	10	2.52	(0.92)	2.2	(0.49)	1.67	(0.52)	0.7	(0.3)		
Normals	11	2.04	(0.76)	1.7	(0.6)	1.12	(0.33)	1.0	(0.55)		
CVT	5	0.98	(1.18)	0.58	(0.75)						
PT	10	0.63	(0.53)	0.38	(0.35)						



4.1:5

Relation between compression pressure (abscissa) and maximal frequency of the compression sound (ordinate) obtained from the posterior tibial vein in 5 healthy test subjects.

ously. With this compression device augmented signals were obtained at all levels. The cuff was attached at the site where manual compression is usually applied. While increasing the applied pressures, the maximal frequencies were recorded. The results of the examination of the PTV compression signal are shown in fig 4.1:5. With 5 mm Hg compression, a maximal value of averagely 1.8 KHz (SD 0.6) was obtained, gradually increasing to 6.5 KHz (SD 0.6) when 40 mm Hg was applied. The value obtained at 10 mm Hg (2.6 KHz, SD 0.5)approaches the value usually obtained by manual compression. The average values obtained at the different levels are listed in table 4.1:II. At all levels a steady increase in maximal frequency is obtained with increasing pressure. The differences in maximal frequency between the different levels are likely to be caused by the distance between cuff and Doppler probe, and the relatively small cuff (15 cm) used to compress the calf in comparison to the large cuff (22 cm) for upper thigh compression.

4.1.3.c The distal compression sound

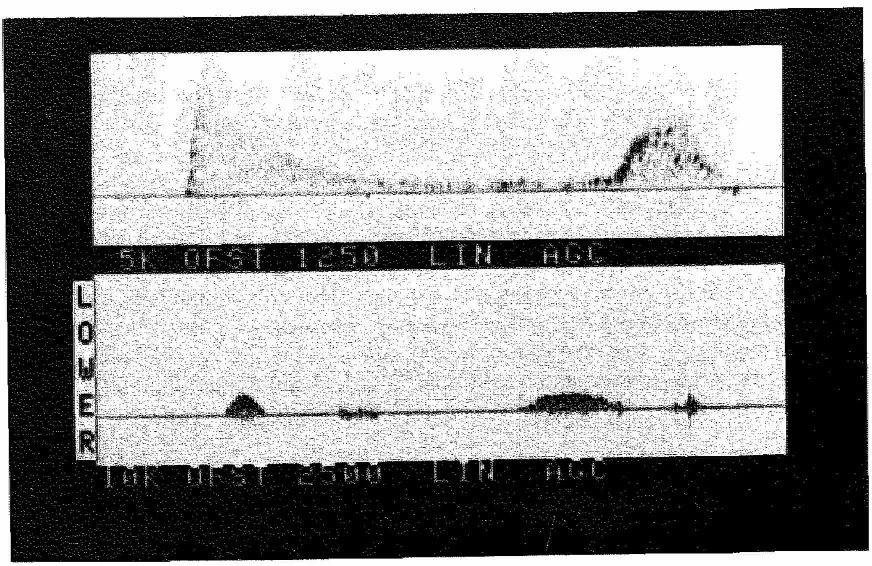
While examining the CFV, a distal compression sound was not obtained in 2/5 subjects, and a pressure of 20 and 30 mm Hg was required to obtain augmentation in the other subjects. Again the cuff used to squeeze the calf was small compared to the thigh cuff, being 15 and 22 cm respectively. In the routine situation where manual compression is used an upward motion of the hand is often required to obtain augmentation of the signal. The difficulty in transmitting a flow wave along the length of the femoral vein is caused by the collapsable nature of veins, in particular in a recumbent position. On compression of the calf veins, the displaced blood will first distend the collapsed femoral vein to a certain degree, before a flow wave will reach the Doppler probe over the CFV. As a result, a rather large volume displacement is required, in order to obtain velocity augmentation and an appreciable Doppler sound at the CFV. In the symptomatic patient firm compression has to be exerted on a painful limb, with the possibility of dislodging a thrombus. Hence the distal compression sound is unreliable, probably dangerous and therefore of limited significance.

4.1.3.d Influence of deep venous thrombosis

In symptomatic patients with a normal venogram, the average value of the PTV A1 peak frequency is slightly less (1.9 KHz, SD 0.7) than that of the test subjects. This difference could possibly be due to age, vasospasm, edema or an increased tissue pressure, but is not significant with PT, the A1 sound obtained from the PTV is significantly different from that of patients without DVT and test subjects, with an average peak frequency of 1.02 KHz (SD 0.5) ($p<0.001$) (fig 4.1:6). In 2/5 of those patients with CVT, the maximal frequency was distinctly lower when the affected leg was compared with the unaffected.
However, this number is too small to be of significance. In 3 patients with proximal obstruction but patent peripheral veins, a normal compression sound was obtained, with a maximal frequency of 1.8 KHz (SD 0.2).

4.1.4.a The decompression signal.

The decompression sound was obtained in all test subjects over the PTV, PV and BV. When obtained from the PTV, the A2 sound has a very distinct pattern. On decompression of the calf muscles, the A2 sound gradually fades away with an average duration of 2.2 seconds (SD 0.5)(fig 4.1:6).



4.1:6

Decompression (left) and compression (right) sounds obtained from the posterior tibial veins of the normal (upper tracing) and thrombotic limb (lower tracing) of a patient with proximal thrombosis.
Note the descreased duration of the pathological decompression sound and the low frequency combined with increased intensity of both augmented sounds.

When obtained from the larger PV and BV, this pattern was not observed, the average duration being 0.7 (SD 0.3) and 0.95 (SD 0.9) seconds respectively. (table 4.1:I)
The multiple capacitance veins of the calf represent a larger volume than a single large bore vessel such as the femoral and brachial vein. Presumably, the duration of the decompression signal reflects the amount of blood which has been displaced. As a consequence, this characteristically long-lasting decompression signal might not only reflect patency of the PTV but patency of the other crural and muscular calf veins as well.
The peak frequency of the A2 sound obtained from PTV and BV are in the same range as those of the compression signal, 2.5 KHz (SD 0.9) and 2.1 KHz (SD 0.9) respectively. The frequency of the PV decompression sound is 1.7 KHz (SD 0.5), which is significantly less when compared to the PTV or BV decompression sound ($p < 0.001$). This is explained by the deep localisation of the compressed femoral vein and the smaller amount of displaced blood when compared to the capacitance veins of the calf.

4.1.4.b Relation between pressure and maximal frequency

Decompression sounds were also obtained from the PTV by means of a sphygmomanometric cuff around the calf. This procedure was performed in 5 test subjects. The average values of the peak frequency for different pressures are listed in table 4.1:II. In contrast to the observation on the compression signal, the decompression signal does not show a relationship with the congestion pressure. Apparently the driving force is the venous pressure distal to the cuff. This pressure is determined by the arterial inflow. As a result, flow velocity and thus peak frequency will be time, rather than pressure dependent.

4.1.4.c Influence of deep venous thrombosis

The average maximal frequency of the PTV decompression sound in patients with a normal venogram is slightly less (2.04 KHz, SD 0.7) when compared with the test subjects, and so is the duration of the sound (1.7 sec., SD 0.6). This might be due to the same mechanisms mentioned for the compression sound: vasospasm, oedema and increased tissue pressure. In the patients with limited CVT the differences are more pronounced; maximal frequency 0.98 KHz, (SD 0.3), and duration 0.5 sec.(SD 0.8), but not statistically significant ($p<0,1$ and $p<0,05$ respectively). In patients with PT the A2 sound is obviously different from the normal one, both acoustically and on spectral analysis (fig 4.1:6). For 2 patients in whom no A2 sound was obtained, the peak frequency and duration are considered to be zero. Average values for patients with PT are 0.6 KHz, (SD 0.5) and 0.38 sec. (SD 0.3), both values being significantly smaller when compared with the contralateral leg or test subjects ($p<0,001$).

Table 4.1:II
Pressure related maximal frequencies of the compression (A1) and decompression (A2) sound, obtained from different levels (PTV, PV and CFV) with increasing compression pressures. The figures all are average values from 5 test subjects.

		5	10	20	30	40	compression pressure in mm HG
PTV (10 MHz)	A1	1.82	2.63	4.09	5.83	6.5	KHz
VP (5 MHz)	A1	0.92	1.62	2.34	3.07	3.65	KHz
CFV (5 MHz)	A1	1.40	2.44	3.28	4.42	5.14	KHz
PTV (10 MHz)	A2	3.64	4.2	4.1		4.44	KHz

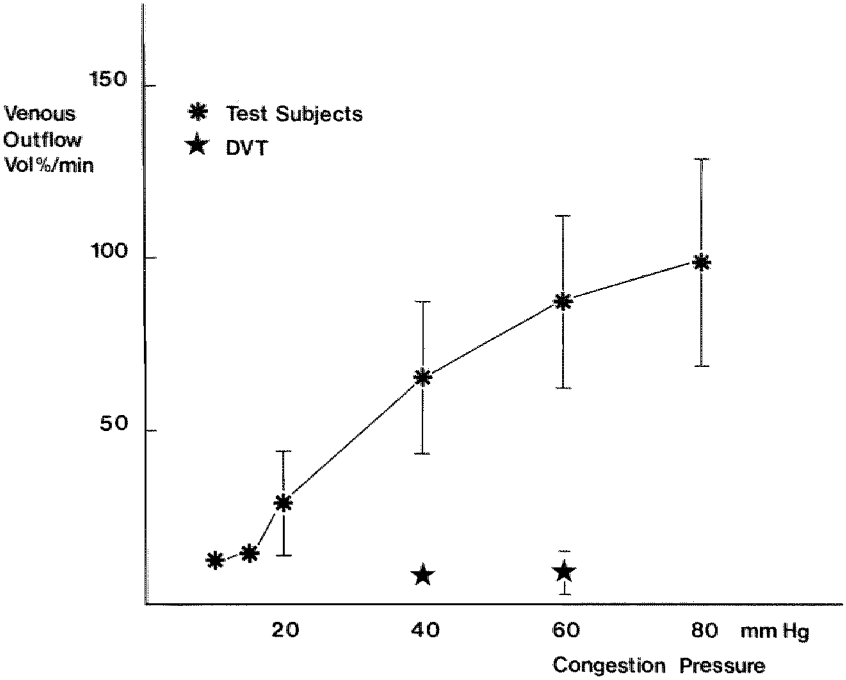
4.2 Influence of various conditions on the result of venous outflow measurement

4.2.1 Introduction

In the present study, volume changes were detected with Mercury Strain Gauges according to Whitney [283,284]. Resistance changes were registered by a plethysmograph constructed by the technical department (v Gerwen).
Unfortunately, both performance and interpretation are subject to large variations between different vascular laboratories. Since the introduction of kenoseography in our clinic, several alterations have taken place too. An important improvement was the introduction of a rapid deflation cuff in 1981 which will be discussed in more detail.
In a pilot study on 10 test subjects and 12 patients with DVT, a congestion pressure of 40 mmHg appeared to be satisfactory in all cases (fig 4.2:1).
Differences between the standard and rapid deflation cuffs were determined in these same test subjects. Because of these results, it was decided to limit the routine examination to one test determination with 20 mmHg, and two determinations with a 40 mmHg congestion pressure. The average values of these 40 mmHg determinations were used for interpretation of venous outflow. The prospective trial was started at this stage.(Ch 5)
In the first part of this study the main concern in the positioning of the patient was to keep the calf and thigh free from the examination couch. This was accomplished by supporting the ankles on a pillow of 27 cm height. In this fashion the knees are extended. As the outflow measured in the test subjects compared favourably with other reported normal values, this did not seem to pose an objection to the method.
At a later stage in the study, however, impeded venous outflow was observed in a test subject and appeared to be due to hyperextension of the knees. A new device was then designed to support the heels, and at the same time, force the limbs into flexion (fig 4.2:2). Although the striking difference observed in the test subjects was not observed in the (elderly) patients, this device has been used for all examinations ever since. A second series of measurements was performed on 10 other test subjects. This study was designed to evaluate the influence of the following items on the obtained venous outflow:

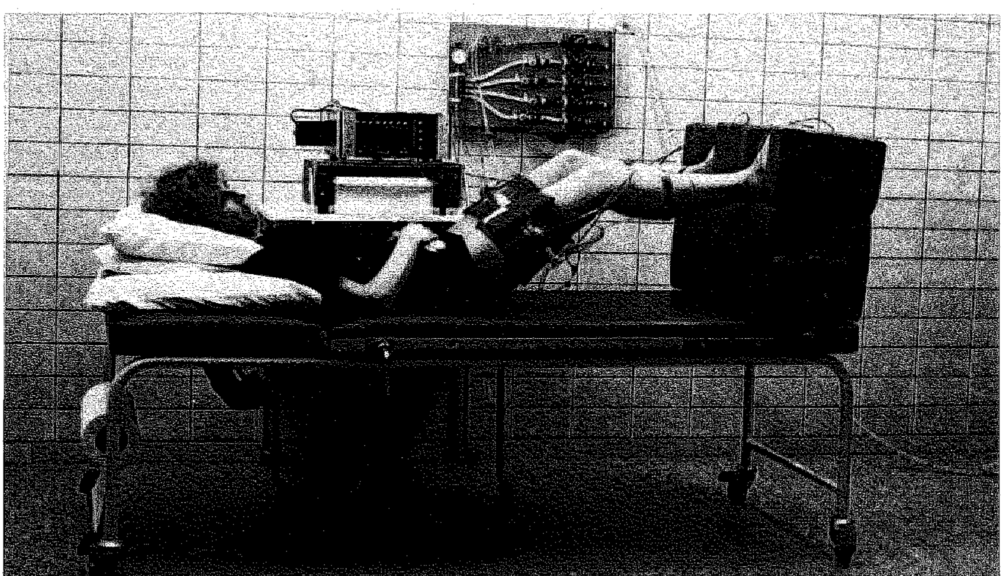
- calculation of venous outflow
- congestion pressure
- positioning of the subject
- rapid cuff deflation
- moment of cuff deflation
- site of measurement
- repeated testing
- biphasic venous emptying

These items will be discussed presently.



4.2:1

Results of a pilot study in 10 test subjects and 12 patients with proximal thrombosis. The maximal venous outflow and standard deviation are shown for increasing congestion pressures.

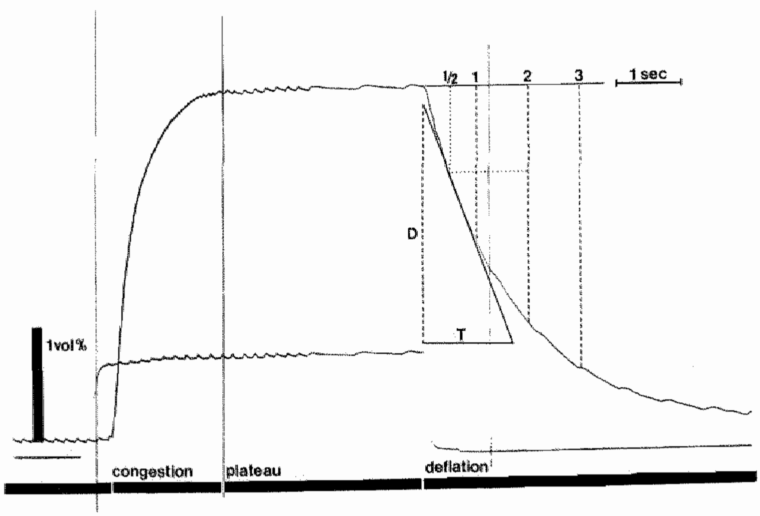


4.2:2

Performance of venous outflow measurement. Congestion cuffs are placed around the midthigh, with strain gauges recording the volume changes at the maximal calf circumference. The legs are supported and forced into flexion by a construction of 27 cm in height.

Table 4.2:I
Average and marginal values of venous outflow and venous capacity in patients with and without DVT as reported by different authors. The applied congestion pressure and calculation method are mentioned in the first two columns. There appear to be considerable differences in the reported results, even between studies in which identical congestion pressures and calculation methods were used.

Author	Year	Congestion pressure	Outflow determination	Normal	CVT	PT	Marginal value Venous Outflow vol%/min	Venous Capacity vol%
Dahn	1968	50 mmHg		875 ml/min		160 ml/min		
Hallbook	1971	50	MVO(vol%/min)	78		23	44	2,2
Barnes	1972	50	MVO	41		12-14	25	
Barnes	1977	50	2 sec	45	20	11-13	20	
Boccalon	1981	50	MVO	28,5	13	9	18	2,2
Bounameaux	1982	50	3 sec.				20	
Abu Rahma	1983	50	MVO	41		12	25	
Deasy	1984	50	MVO	24	17	6-10		
Tripolites	1981	55	½-2 sec.	72		18	30	
Pini	1984	55	MVO	64		21	37,5	2,45
Franzeck	1983	60	MVO	38	32	14	20	
Sakaguchi	1972	80	MVO	87		32		



4.2:3

Standard venous outflow recording.
Volume changes are compared with the calibration mark of 1 vol%. The congestion pressure is indicated by the lower tracing. The congestion phase of the limb had to be drawn artificially because of the high paper speed and the congestion time of 2-3 minutes. After deflation of the congestion pressure, venous ouflow is determined by the tangent to the steep initial part of the tracing (maximal venous outflow), or by determination of the volume decline after 1, 2 or 3 seconds, each of these values being extrapolated to flow per minute.

4.2.2 Calculation of venous outflow

The most precise method for outflow determination is to draw a tangent to the curve directly after release of the congestion pressure. From this line volume displacement is determined and extrapolated to flow per minute (fig.4.2.:3)[7,23,100,279]. This value is the true Maximal Venous Outflow (MVO) and is calculated as follows:

$$\frac{D}{\text{calibration 1 vol.\%}} \times \frac{60}{T} = MVO$$

where:
D= volume decline during T
T= time in seconds

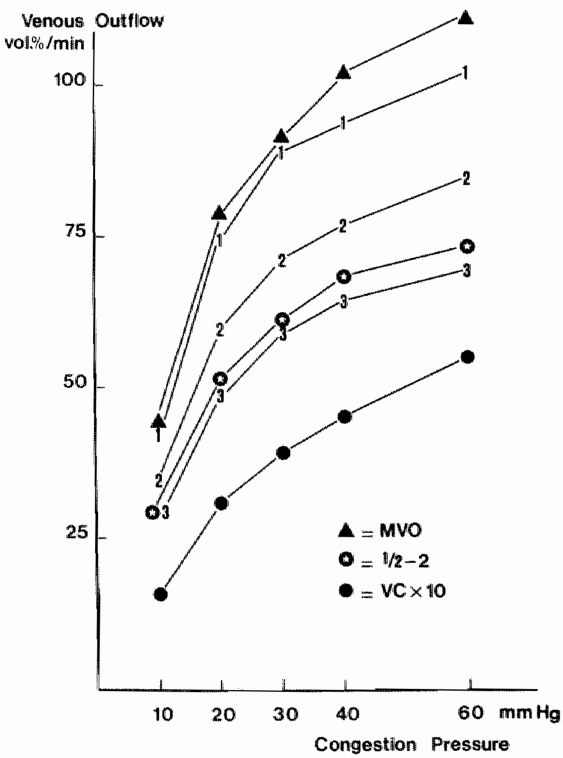
To avoid the disturbances caused by cuff release and the "after drop"(4.2.9), the tangent is obtained after the first half-second as advised by Brakkee[35]. Instead of calculating the slope of the curve it is common practice to measure the volume decline in the first few seconds and extrapolate this value to flow per minute which is less laborious (fig.4.2:3). This determinant is referred to as the "x sec. value". Volume decrease is usually determined at 2 [10,133] or 3 [118,279] seconds after pressure release. Others have determined the volume decrease between 1/2 and 2 seconds, which appeared to be a more constant parameter[52].

4.2.3 Congestion pressure

Congestion pressures being used range from 45 cm H2O (= 32 mm Hg), [118,280] to 80 mm Hg [215] and 200-250 mm Hg when a 3 cm wide congestion cuff was used[20,133]. Wheeler[282] recommends increasing cuff pressure from 45 to 70 cm H2O when borderline results are obtained. Average values of venous outflow in patients with and without DVT, as well as the marginal values reported by different authors, are shown in table 4.2:I. Considerable differences are present between the different studies. Because of the multitude of factors by which the calculated outflow is determined, the effect on one single factor can only be examined when all the others are kept constant. In the present study, different congestion pressures were used subsequently in the same subjects, and venous outflow was determined in various ways from the same tracings. The results are shown in fig. 4.2:4 and table 4.2:II.
As was to be expected from the formula (3.5.4), venous outflow increases in proportion to the applied congestion pressure. Because of the influence of venous compliance, this relation is non-linear[75,82]. As compliance (C=V/P) of a limb decreases with increasing congestion pressure, both volume increasse per mm Hg and venous outflow per mm Hg are less at higher pressures (table 4.2:II). This observation would favour the use of a low congestion pressure.
For a certain congestion pressure, each of the determined figures in fig. 4.2.4 and table 4.2:II could be referred to as "venous outflow", although a considerable difference is obvious. For each congestion pressure, the 3 sec. value amounts to only 60-63% of the MVO, a difference that could easily be ascribed to the presence of DVT, if one were not aware of the different calculation methods used. It is obvious that the congestion pressure and calculation method should always be mentioned in relation to the results obtained.

Table 4.2:II
Average values of different outflow determinations obtained with increasing congestion pressures from the same 10 test subjects.

	10	20	30	40	60	Congestion pressure in mm Hg
MVO	44	78	92	102	111	
1 sec.	43	73	88	93	103	
2 sec.	33	59	70	76	83	vol%/min
3 sec.	27	48	58	64	69	
1/2-2 sec	27	52	61	68	73	
VC	1.6	3.2	3.9	4.5	5.5	vol%
VC/P	0.16	0.16	0.13	0.11	0.09	vol%/mmHg
MVO/P	4.4	3.9	3.0	2.6	1.9	vol%/min/mmHg
P/VC	6.25	6.25	7.69	8.88	10.9	mmHg/vol%



4.2:4

Average values of the venous capacity (VC) and venous outflow determined by different calculation methods (MVO 1, 2, 3 and 1/2-2 second values) obtained with increasing congestion pressures in the same 10 test subject.
Obviously both congestion pressure and calculation method are of significant influence.

4.2.4 Positioning of the subject

As flow is determined by the pressure difference between the calf veins and the inferior vena cava, the position of the limbs and the trunk will be of influence. To promote venous outflow the limbs are usually elevated [7,23,27,100]. Increasing elevation from 6 to 27 cm resulted in an increase of the average MVO from 61 to 72 ml/100 ml/min. [261]. Elevation of the trunk can be expected to have the reverse effect.
It is generally advised to examine the patients with the knee in flexion, to avoid compression of the popliteal vein against the dorsal rim of the tibia [7,27,118,261].
Wheeler [278] observed a diminished reaction of the respiratory cycle in 14/50 limbs of healthy volunteers when the limbs were kept straight. However, in the one report concerning venous outflow, no difference was observed between values obtained with the limb either in flexion or extension [60].
To determine the influence of flexion and extension in the knee joint, in the present study, the legs were supported and held in flexion by a special supporting device (fig.4.2:2). Measurements were performed in both positions on the same occasion, using a congestion pressure of 30mm Hg. With extended knees the MVO amounted to 47.7 vol %/min. (SD 21.6). When the legs were forced into flexion MVO values increased, in all cases, to an average value of 91.6 vol %/min. (SD 25) ($p<0.001$). However, all test subjects were under 30 and hyperextension is less likely to occur in the more aged patient with DVT. Therefore, these measurements were repeated in 10 patients being controlled for DVT. In these patients the average value for MVO amounted to 64 vol %/min. (SD 36) and 69 vol %/min. in the previously affected limbs, while it amounted to 75 vol %/min. (SD 23) and 82 vol %/min. (SD 30) in the unaffected limbs for measurements in extension and flexion respectively (fig. 4.2:5 , not significant). It appears that the position of the examined limbs is of minor importance in the elderly patient. However, hyperextension of the knee may disturb the venous outflow considerably in the (younger) individual patient. Therefore, examination with the legs in flexion should be performed as a routine.

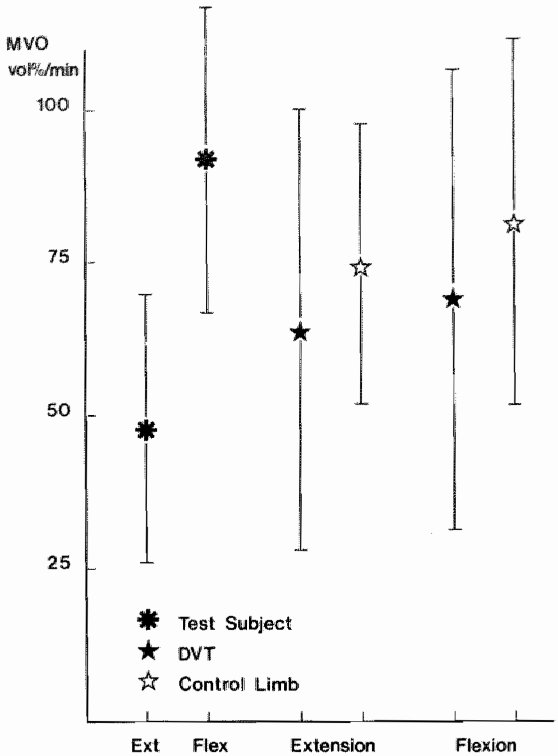
4.2.5 Rapid cuff deflation

Several authors have stressed the influence of prompt cuff deflation. The influence of cuff deflation can be illustrated by dividing resistance (R in formula 3.5.10:5) into intrinsic resistance due to properties of the venous system, and extrinsic resistance due to sustained cuff pressure. Therefore, venous outflow can be expressed as follows:

$$\mathrm{MVO} = \frac{P}{R\ \mathrm{ven.} + R\ \mathrm{cuff}\ t}$$

where:
MVO = Maximal Venous Outflow
P = Venous pressure
R ven = Venous resistance
R cuff t= resistance t seconds after cuff deflation.

This formula shows, that venous outflow does not reflect the venous resistance until cuff resistance has worn off completely. Cuff deflation is determined by the diameter of the tube connection [10,27,35,253,261], and by deflation taking place through common or separate tubes [261]. Deflation can be accelerated by connecting the tubes with a negative pressure chamber [27,35]. Application of different deflation systems in the same test subjects improved the venous outflow from 39 to 100 ml/100 ml/min and from 35 to 75 ml/100 ml/min in two recent studies [27,261].



4.2:5

Average values and standard deviation of the maximal venous outflow in test subjects and patients with previous DVT, obtained with the legs in extension, and subsequently forced into flexion by the device in fig. 4.2:2
An increase in venous outflow occured in all test subjects when the legs were forced into flexion, while it was less pronounced in the patients, and did not occur in all of them.

4.2:6

Rapid deflation cuffs, which are opened by a pneumatically driven cylinder, while a valve is opened simultaneously to facilitate evacuation of the air from the cuff.

To avoid this disturbance, a rapid deflation cuff was constructed[269]. The principle is threefold:

- An 18 x 80 cm conical shaped cuff is reinforced by a thin metal plate. As expansion of the cuff is now limited towards the encircled limb, a smaller volume of air is needed in order to exert a certain pressure.
- The cuff is secured by a special clasp which is opened by a pneumatically driven cylinder. Upon opening, the cuff is immediately disengaged from the limb.
- Simultaneous with the clasp a valve is opened allowing the air to escape directly from the cuff (fig. 4.2:6).

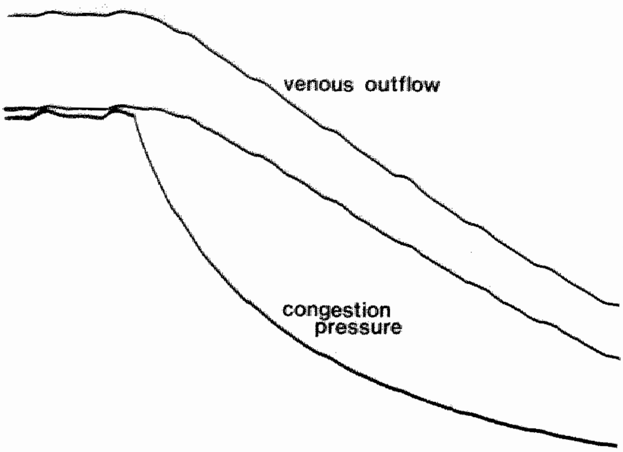
Pressure measurements taken directly from the inflation tube to the rapid deflation cuff showed a 85% decline (76-90%, n = 7) in cuff pressure in the first 0.1 sec. (fig. 4.2:7).
When a standard sphygmomanometric cuff was used, only a 10% decline was observed in the first 0.1 sec. while it took 3.2 seconds before a pressure fall of 85% had been reached (fig. 4.2:7) Outflow measurements were performed with both the standard and the rapid deflation cuff in 10 test subjects and 9 patients with DVT.
In 10 test subjects a congestion pressure of 60 mm Hg was used. The observed MVO value increased from 27.8 vol %/min. (SD 8.0) with a standard cuff, to 86.4 vol %/min. (SD 25.4) with the rapid deflation cuff ($P<0.001$, fig. 4.2:8).
In the patient examination a congestion pressure of 40 mm Hg was used. In the unaffected leg, the MVO was 25.6 (SD 10) and 68.4 (SD 32) respectively, whilst it was 14.8 (SD 8.5) and 34 (SD 22) in the affected limb (fig. 4.2:8)
To evaluate the sensitivity for DVT the left/right ratio was calculated. This ratio is referred to as the Thrombosis Index (TI) (Ch IX). The average TI of all 9 patients was 68% (SD 45) with the standard cuff, compared to 80% (SD 48) with the rapid deflation cuff. In 6/9 patients the TI was more pronounced with the R.D. cuff.

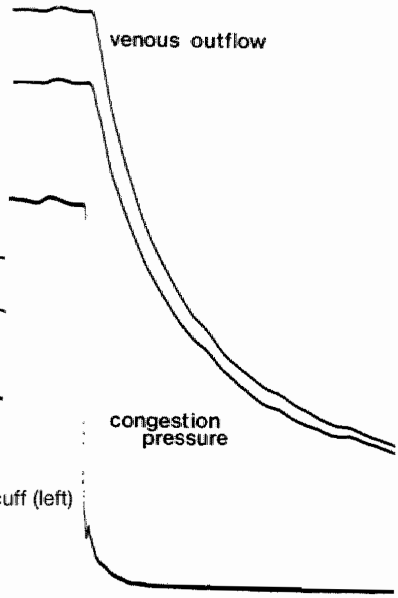
4.2.6 Moment of cuff deflation

Venous pressure can only be assumed to equal cuff pressure when the plateau phase is awaited for. It is common practice though to release cuff pressure at a predetermined time, usually 45 sec. [20,279,280] or 2 min. [52,118,199,261,282]. Using this approach venous pressure will not be equal to cuff pressure. Venous pressure may even be different for both limbs in the same subject, and again be different on separate occasions. To determine the influence of premature cuff deflation, recordings from 10 test subjects and 25 patients with proximal thrombosis were reviewed.
Venous congestion was determined at 45 sec and 2 min, and expressed as the percentage of the finally obtained congestion, which was obtained after an average time of 3.2 min :

VC 45 sec/ VC and VC 2min/ VC.

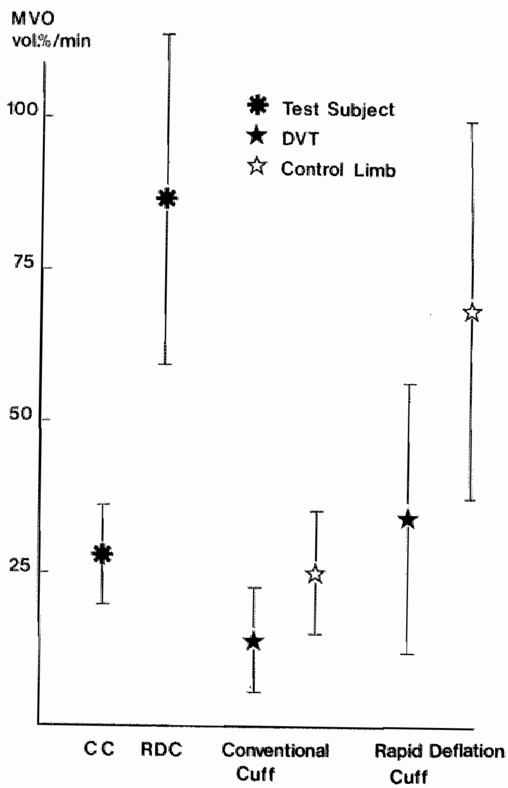
In the test subjects congestion at 45 sec. and 2 min. amounted to 43% and 86% of the ultimately achieved VC. In the patients, congestion at 45 sec. amounted to 84% in the thrombotic compared to 66% of the ultimately achieved VC in the normal limbs ($p<0.001$)(fig. 4.2:9). As outflow is proportional to venous congestion, cuff release after 45 sec. will significantly alter the ratio between the thrombotic and normal limb,thereby affecting the sensitivity of the test. Since the plateau phase was not waited for as carefully in the patients as in the test subjects, the 2 min. venous congestion almost equals the ultimately attained value for both thrombotic and normal limbs. The difference still occurring in 7 patients is not significant ($0.1<p<0.5$). Therefore, although cuff deflation at 2 min. may not provide a scientifically correct value for the MVO, it seems appropriate in clinical practice. Cuff release after 45 sec. will significantly alter the sensitivity of the test and is fundamentally wrong.
It is not surprising that sensitivity and specificity improved when occlusion time was increased from 45 sec. to 2 min.[120].





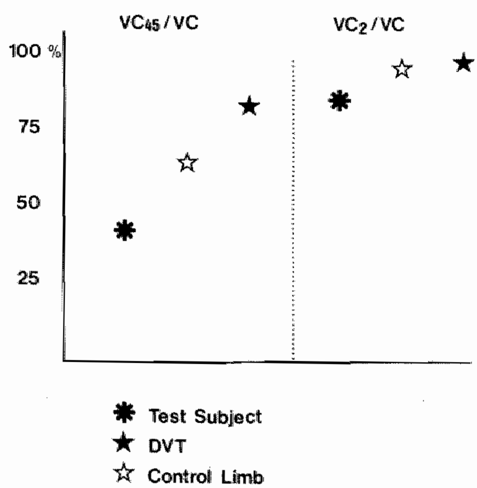
4.2:7

Venous outflow and cuff pressure, registered from a standard cuff (left) and from the rapid deflation cuff (right).



4.2:8

Results of maximal venous outflow determination in test subjects (10) and patients (9), using standard and rapid deflation cuffs.



4.2:9

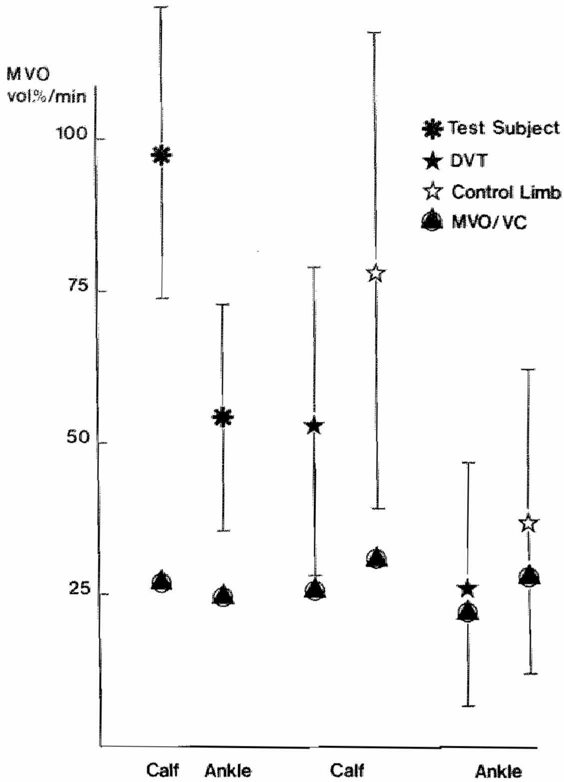
Average values of venous capacity in 10 test subjects and 25 patients with proximal thrombosis, determined after 45 seconds and 2 minutes of venous congestion and expressed as the percentage of the ultimately obtained venous capacity. After 45 seconds the thrombotic limbs have reached a significant larger amount of the finally obtained volume increase, as compared to the control limbs.

4.2.7 Site of measurement

Strain gauges are usually applied at the site of maximal calf circumference. In cross-section, a circular circumference would be approached the best [284]. Furthermore, the ratio of soft tissue and bone, and thus the distensibility, is optimal. However, outflow disturbance will only be detected when localised proximal to the strain gauge.
In order to increase the sensitivity for calf vein thrombosis it would seem more appropriate to place the strain gauges distally. For this purpose investigations were made as to whether measurement at a level 5 cm above the malleoli would result in a valid outflow recording. Measurements both at the maximal calf circumference and 5 cm above the malleoli were performed on the same occasion. Suitable recordings at the distal level were obtained in all cases. The total increase in volume (VC) amounted to 2.3 vol (SD 0.6) at the ankle and 3.6 vol%/min.(SD 0.8) at the calf ($p<0.001$). The MVO amounted to 53.8 vol %/min. (SD 18.5) and 97 vol %/min. (SD 24) respectively ($p< 0.001$), (fig.4.2:10).
As the outflow is directly related to volume increase:
MVO = E x VC/R
the ratio of these two values MVO/VC could be a better indication of the outflow properties at different levels. The MVO/VC ratio in our subjects amounted to 23.4 vol %/min/vol % at the ankle, compared to 27 vol %/min/vol % at the calf. Apparently there is only a slight decrease in outflow per volume increase, with distal measurements. According to Poisseuilles law this difference can easily be ascribed to the increased length of the outflow tract. It appears that peripheral outflow measurement is possible, but will it be useful in clinical practice as is sometimes reported? [23,100]. To answer this question the same examination was performed in 7 patients with venographically confirmed calf vein thrombosis.
In these patients the following results were obtained:

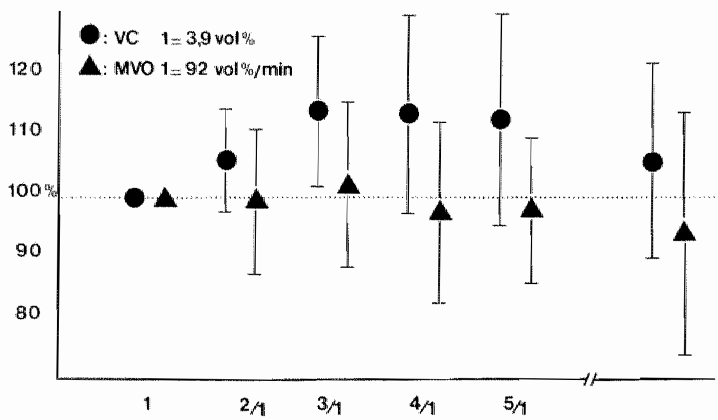
	MVO/VC calf	MVO/VC ankle
affected limb	25.8 (SD 11.8)	22.3 (SD 14.9)
unaffected limb	30.7 (SD 19.2)	27.7 (SD 17)

Similar to the test subjects, the outflow per volume increase is only slightly less at the ankle in both the affected and the unaffected limb. Therefore, this difference cannot be ascribed to the presence of CVT. Another way to detect an increased sensitivity for CVT would be to compare the left/right ratio or Thrombosis Index (TI) of both levels (Ch IX). If the ankle were to be the preferential level of measurement, the TI would have to be more pronounced at this level.
However, there was a difference in favour of the ankle measurement in only 1/7 of the patients. The average value amounted to 53% at the calf and only 45% at the ankle. Thus, disappointingly, this study does not supply any evidence in favour of measurement at a more distal level than the level at which it is usually performed. This finding is in agreement with the results of others [7,85].



4.2:10

Results of venous capacity and maximal venous outflow obtained from the maximal calf circumference and the ankle, in 10 test subjects and 7 patients with calf vein thrombosis. Both VC and MVO are considerably less when determined from the ankle, whilst the ratio of MVO and VC appears to be equal for both levels.



4.2:11

Results of repeated determination of the venous capacity and maximal venous outflow in 10 test subjects. The values of the initial recordings are considered to be 100%, whilst the subsequent recordings are expressed as a percentage of the initial occasion, whilst each subject returned on a second occasion for the last determination.

4.2.8 Repeated testing

It has been reported that repetitive measurements would increase the VC and VO by predistending the veins [52,118,145,261]. These increased values would enhance the sensitivity for DTV. In an attempt to confirm these results each test subject examination was started with 5 consecutive measurements using a congestion pressure of 30 mm Hg. For each graph the plateau phase was awaited before cuff deflation. After each graph a stable base line was reached before repeated cuff inflation. The VC and MVO of each graph is expressed as a percentage of the first recording:

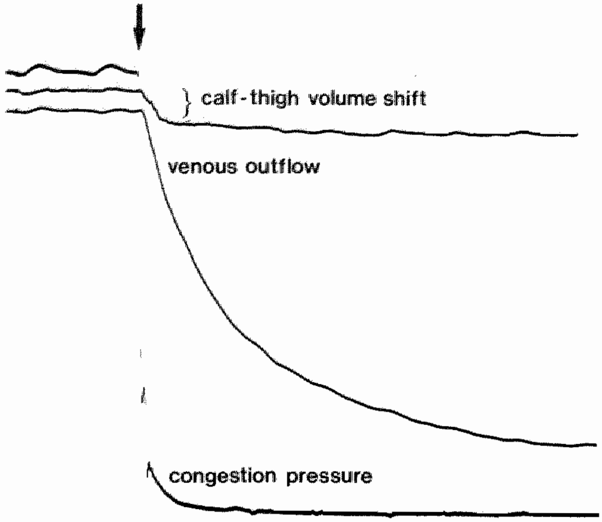
$VC_N / VC_1 \times 100\%$

$MVO_N / MVO_1 \times 100\%$

In this way an increase in consecutive measurements will result in a value over 100%.
For venous capacity, the second measurement and subsequent measurements are significantly higher ($p<0.01$) when compared with the first one. Even VC3 is significantly greater than VC2 ($p<0.05$) after which VC4 and VC5 remain constant. However, no alterations were observed in the average value of subsequent outflow determinations (fig. 4.2:11).
To evaluate the natural course of DVT and the influence of treatment, kenoseography can be repeated on different occasions. For this purpose too, differences as a result of spontaneous changes or errors in performance of the test, should be taken into account. All test subjects were requested to return on a second occasion. All examinations were performed by the same person. The difference between first and second examination is expressed in the same way as for the repetitive measurements. The results are shown in the same figure. The mean value of these second measurements amounted to 96% (SD 19%) of the first obtained MVO. For the individual subject, the possibility of spontaneous alterations of 38% (2 x SD) of the first recording should be borne in mind. Interpretation of a shift in the MVO during the course of DVT treatment should be made cautiously with regard to this large range of normal variations.

4.2.9 Biphasic venous emptying

Displacement of venous blood into the previously compressed femoral vein has been known as the "after drop" since 1955 [89]. A biphasic pattern of venous outflow was described by Zetterquist [291] in a patient with isolated iliac vein thrombosis, and was later confirmed [35,153]. Iliac vein obstruction can be caused by either thrombosis or tumour compression in the pelvis. In this situation, a fast volume decrease will occur directly after deflation of the cuff. When blood flow reaches the high resistance segment of the iliac vein, flow will decrease abruptly.
This gap was reproduced artificially by placing two cuffs around the thigh and releasing only the distal one (fig. 4.2:12). This manoeuvre was performed 6 times in three different subjects, using a congestion pressure of 60 mm Hg.
The volume gap amounted to 0.21 vol % (SD 0.04) which is equal to 8.3% (SD 3.1) of the total venous capacity in these subjects. The gap was filled in 0.25 sec. (SD 0.06) never exceeding 0.3 seconds. Therefore it seems reasonably accurate to determine the MVO at 0.5 sec. after cuff deflation, as was done in all patients and test subjects



4.2:12

Influence of the pressure release of a congestion cuff, when a second, more proximal cuff is present in order to prevent venous outflow. The limited volume decline (↓) reflects the volume of the venous segment directly compressed by the distal cuff.

V Prospective study on the diagnosis of deep venous thrombosis in 178 consecutive patients

5.1 Introduction

The present investigation has grown from the experience with non-invasive examination for arterial disease by means of Doppler ultrasound. Since 1972 this has been a routine examination for all patients with intermittent claudication in the St. Joseph Hospital in Eindhoven. Gradually, attention has been directed to the venous Doppler signal and the possibility of an accurate diagnosis of Deep Venous Thrombosis (DVT) with this method. When, in 1978, an appropriate space became available to establish a vascular laboratory venous outflow measurement (Kenoseography) was added to the diagnostics for DVT. Early in 1981 the performance of these examinations was assigned to one person. In a lecture for the medical staff and general practitioners, the inaccuracy of the clinical diagnosis of DVT was stressed. The attendants were invited to refer their patients with signs and symptoms of DVT to the vascular laboratory, for non-invasive examination. A sample taken by the "Trombose Dienst Eindhoven" in september 1983 showed that 17 out of 23 patients (73.9%) treated with anticoagulants for DVT had been examined in the vascular laboratory.

5.2 Study Design

In february 1982 a prospective study was started to evaluate the diagnostic criteria and to establish the accuracy of both non-invasive examinations when compared to venography. The condition for admission to the study was that a patient was referred because of clinically suspected DVT or pulmonary embolism (PE). All patients were examined according to a standard form. Special attention was paid to the patient's history and the physical examination. Subsequently a Doppler ultrasound examination was performed by the same investigator. Kenoseography was performed by either the investigator or the vascular laboratory technician. All Kenoseograms have been reviewed by the author. Whenever possible, a venogram was obtained within 24 hours. It was decided to end the trial on 01-01-1984, after which date venography has only been performed on special indication.

Table 5.3:I
Composition of the examined population according to the reason for referal, and the different diagnostic tests which have been performed.

Clinical suspicion of DVT	193	199	Venography performed	178	Complete physical & Doppler examination	164	Kenoseography performed	161
					No complete physical & Doppler examination	11	Kenoseography performed	10
Clinical suspicion of DVT & PE	6		No venography performed	21				
Clinical suspicion of PE without symptoms or signs of DVT	14		Venography performed	14				
Axillary vein thrombosis	10		Venography performed	9				
Abnormal non-invasive test result in contralateral limb	5		Venography performed	5				
Total	patients 223		venograms	206				

5.3 Patients

During the trial period 223 patients were admitted to the study. The composition of this population, according to the reason for referral, is shown in table 5.3:I. Venography was performed in 178 patients with a presumptive diagnosis of DVT, but was unsatisfactory in 3 of them. The remaining 175 patients constitute the core of this study. A complete physical and Doppler examination was performed in 164 of the venographically examined patients. Both Kenoseography and venography were performed in 171 patients. Finally 161 patients were examined using all three methods.
In 21 of 199 patients with clinically suspected DVT no venogram was obtained. In 6 patients puncture of a vein on the dorsum of the foot failed. A cut down was not performed in these cases. In 15 other patients venography was not attempted for various reasons, such as pregnancy, poor general condition or disapproval of the referring physician.

In addition there were 14 patients with clinical signs of pulmonary embolism without signs or symptoms of DVT, 5 patients in whom contralateral DVT was suspected on follow-up examination in the vascular laboratory and 10 patients who were examined for axillary vein thrombosis.

5.4 Statistical aspects

All issues wil be compared with the results of venography, for which the following terminology is used:

True Positive (TP) = feature present, venogram indicating DVT
False Positive (FP) = feature present, venogram indicating no DVT
True Negative (TN) = feature absent, venogram indicating no DVT
False Negative (FN) = feature absent, venogram indicating DVT

$$\textit{Sensitivity} = \frac{TP}{TP + FN} = \frac{\textit{Number of true positive cases}}{\textit{Total number of cases with disease}}$$

$$\textit{Specificity} = \frac{TN}{TN + FP} = \frac{\textit{Number of true negative cases}}{\textit{All cases without disease}}$$

$$\textit{Positive predictive value (PPV)} = \frac{TP}{TP + FP} = \frac{\textit{Number of true positive cases}}{\textit{All cases with feature present}}$$

$$\textit{Negative predictive value (NPV)} = \frac{TN}{TN + FN} = \frac{\textit{Number of true negative cases}}{\textit{All cases without feature present}}$$

For a true appraisal of the obtained values of the so called diagnostic indices (sensitivity, specificity, predictive value of a positive test) it is necessary to realize that the figures arise from measurements obtained from patients who happened, more or less by chance, to have their complaints within the period of the study and lived in the vicinity of our clinic.
The patients should therefore be considered to be a sample taken from a larger population. The obtained values are estimates of the corresponding true value in the population of all patients referred on suspicion of DVT, and hence subject to chance variation. To quantify the extent of this variation confidence intervals for the most important diagnostic indices are provided.
The intervals are determined so that they will contain the true value with 95% certainty.

Frequently predictive values are found which differ only little from the a priori chance. In these instances, and also when the number of patients concerned is small, one would want to test whether the observed difference could have arisen by chance alone.
For this purpose a x^2 test is used. When the p-value did not exceed 5%, we assumed the difference to be real.

In a number of situations, measurements were obtained from patients (or healthy test subjects) under two different conditions. The effect of the condition was then tested using the signed ranks (Wilcoxon) test. The same test was applied when measurements from affected legs were compared with those of the healthy leg of the same patient. When patients were compared with non-patients, the ranksum test (Mann-Whitney test) was employed.
We have chosen to apply these so-called nonparametric tests instead of the more familiar t-test of Student, since the conditions for that test, a nice (Gaussian) shape of the frequency distribution and preferably equal standard deviations, were often violated.

5.4.1 The choice of measurements and their marginal values

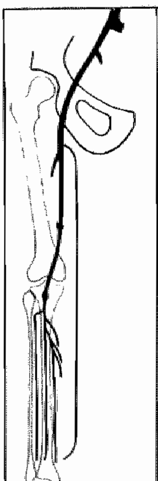
In any diagnostic test which yields a number as its outcome (Kenoseography), a threshold or marginal value must be determined in order to separate the pathological values from the normal ones. When there is any overlap of the groups, a trade-off between sensitivity and specificity is unavoidable. A 100% sensitive test can be obtained, for instance, by choosing a very high threshold. Yet, in that case specificity will be low which renders the test worthless. The cut-off point could be chosen in a more realistic fashion; to maximize the accuracy the sum of sensitivity and specificity, or to minimize the expected cost of misclassified patients. These methods would lead to different cut-off points.
We have chosen the thresholds here so that the accuracy of the test is maximized. When the cost of misclassified patients is (roughly) equal for both kinds of classification errors, and the prior probability of having DVT is about 50%, this threshold also minimizes the cost of misclassification.

Table 6:I
Results of venography in different sub-groups, according to the reason for performance of the examination.

Venogram	Clinical DVT	Clinical PE	Contralateral DVT by non-invasive examination	Total
Normal	59	6	–	65
Calf vein thrombosis	29	2	–	31
Proximal thrombosis	76	4	3	83
Previous thrombosis	6	1	1	8
External compression	5	–	1	6
Unsatisfactory	3	1	–	4
	178	14	5	197

Table 6:II
Incidence of different diagnostic criteria of venography, in patients with varying degrees of DVT.

	Persistent filling defects	Railway sign	Abrupt stops	Non filling	Collateral flow
Calf vein thrombosis	26/31 83.8%	3/31 9.7%	6/31 19.4%	4/31 12.9%	0/31 0%
Popliteo femoral thrombosis	34/49 69.4%	22/49 44.9%	29/49 59.2%	33/49 67.3%	13/49 26.5%
Iliac vein thrombosis	22/34 64.7%	12/34 35.3%	22/34 64.7%	22/34 64.7%	26/34 76.5%
Total	82/114 71.9%	37/114 32.5%	57/114 50%	59/114 51.8%	39/114 34.2%



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6:1

Extension of venous thrombosis when present on 188 venograms. Distinction is made between the crural, popliteo femoral and iliac segments.
For each level, the veins were considere to be:
Normal (N)
Partially Occluded (O)
Completely Occluded (C)
In 6 patients external compression of the iliac (5x) or popliteal vein (1x) was observed. (EC).

VI Venography

6.1 Introduction

Venography was performed in the radiology department, according to the method off Rabinov [261] and Lea Thomas [152] (Ch 3.2.). A venogram was obtained in 178 patients with clinical signs of DVT, 14 patients with clinical signs of PE, and in 5 patients the contralateral limb was examined because non-invasive examination yielded abnormal results. The results of these venograms are arranged according to the reason of their performance in table 6:I.
All venograms have been reviewed by one of the radiologists (H. van den Borne), with regard to the diagnostic criteria, and with regard to the extension of the thrombotic proces when present. Knowledge of the usual appearance and extension of DVT, would be an aid in the interpretation of the non-invasive tests.
As four venograms were judged to be unsatisfactory, the accuracy of this examination can be regarded to be 193/197 = 97.9%

6.2 Distribution of diagnostic criteria

For interpretation of venography, diagnostic criteria were used according to Rabinov [206.] The occurrence of these signs in patients with calf vein and more proximal extending thrombosis is shown in table 6:II.
It shows that the radiologic appearance of DVT differs according to the extension of the thrombus. In the case of CVT, limited filling defects and the railroad sign are present in most cases (29/31 = 93.5%), while abrupt stops occur occasionally (6/31 = 19.4%), non-filling is rare (4/31 = 13%) and collateral flow does not occur.
In the case of PT, non-filling (55/83 = 66.2%) and abrupt stops (51/83 = 61.4%) occur more frequently. The appearance of popliteo-femoral and of iliac vein thrombosis is almost identical. An exception should be made for collateral flow which was observed in 13/49 (27%) and 26/34 (77%) cases, respectively.

6.3 Extension of deep venous thrombosis

The extension of the thrombotic disease is shown schematically in fig 6:1. For this purpose the calf veins are classified either as normal (N), as harbouring thrombi in 1-2 (P=partial occlusion) or as harbouring thrombi in 3 or more crural veins (C=complete occlusion). The popliteo-femoral and iliac vein traject are regarded as normal (N) partially occluded (P) or completely occluded (C).
Several observations can be made from this scheme.
– In the case of CVT, the thrombus is usually (29/31 = 93.5%) limited to one or two vessels. Complete occlusion of the calf veins has not been observed without involvement of the popliteal vein.
– Thrombosis in the calf veins without proximal involvement was present in 31 (16%) patients. Thrombosis in the proximal veins was present in 91 (47%) patients. Of these patients, all but 15 (8%) had calf vein involvement. Of these 15 patients 5 had an obvious local cause for the occurence of DVT, i.e. a total hip arthroplasty in one and femoral vein catheterisation in four. Five other patients responded to the usual pattern of a "pelvic vein spur"; they were relatively young and had no obvious cause or only minor surgery prior to development of symptoms. They all had isolated left sided iliac vein thrombosis. In 1 patient there was no relation between the calf vein and iliac vein thrombosis, and 1 patient had external compression of the iliac vein associated with several small calf vein thrombi. Therefore thrombosis could have originated from the calf veins in 108 (76+31+1) patients, from the valve pockets of the femoral and iliac vein in 6 and from a pelvic vein spur or local endothelial damage in 10 other patients.

It is also worth noting that in case of an isolated iliac vein obstruction, thrombus was present as often (5x) as external compression (5x). In these patients venography seems mandatory in order to reveal the nature of the obstruction.
The extension of DVT in these patients is in agreement with the general opinion that thrombosis usually arises from the calf veins.

6.4 Untoward results

Of the 137 patients asked, 17 clearly stated having experienced venography as "unpleasant" while it was regarded as "non disturbing" by 117 others. Three patients gave no clear response.
A "contrast phlebitis" was observed in 3 patients. These patients experienced an increasing tenderness in the calf and along the course of the femoral vein after venography had been performed. These complaints subsided within a day. Repeated non-invase examination in these patients showed no alteration when compared to the previous examination.

In 2 patients a temporary rise in temperature and concurrent hypotension occured shortly after venography had been performed. These patients responded favourably to intravenous fluid administration.

Venography was performed as an outpatient examination in 35 patients, without untoward effects. Serious complications such as anaphylactic reactions, skin necrosis due to extravasation of contrast or clinical overt PE during the examination have not occured in either hospitalized or out-patients.

VII Clinical diagnosis

7.1 Introduction

Each examination always started by taking the patient's history, paying special attention to the following issues:
- age and sex
- major complaints
- duration of symptoms
- predisposing causes for DVT or an other explanation for their symptoms
- previous thrombosis
- institution of therapy.

For the physical examination all garments should be removed from the legs. The highest pulse rate (Mahlers sign) and temperature (Michaelis sign), on either the day of admission or the day of referral, were obtained from the patient's chart. These data are lacking in the out-patients and in some cases where they were not supplied by the chart.
On inspection of the legs, colour changes such as erythema or cyanosis and venous dilatation are noted, as well as skin changes due to venous hypertension.
Differences in skin temperature are detected by palpation with the dorsum of the hand. Pretibial pressure of the thumb is used to reveal the presence of edema when this is not obvious on inspection. Limb circumference is measured 15 cm. above and below the knee joint.
The calf muscles are palpated by placing both hands around the leg in order to judge their consistency. The course of the femoral vein is examined for local tenderness.
Homans' sign is elicited by gentle dorsoflexion of the foot, while the knee is held in flexion.
The Lowenberg sign consists of calf pain when a sphygmomanometer cuff around the thigh is inflated. In this study patients were requested to report pain during kenoseography with a cuff pressure of 40 mmHg during 2-3 minutes.

A complete patient history and physical examination was obtained in 164 patients with a clinical diagnosis of DVT. This population consisted of 64 males and 103 females ranging in age from 19 to 88 years (median 63 years).
All patients are classified according to the result of venography.

Normal	58	no DVT
Previous thrombosis	5	
External compression	5	
Calf vein thrombosis	29	DVT
Popliteo-femoral thrombosis	38	
Iliac vein thrombosis	29	
Unsatisfactory venogram	3	
Total	167	

The 10 patients with previous thrombosis or external compression are regarded as "no acute DVT" and are therefore classified as "normal" for interpretation of the clinical signs.
The sensitivity, specificity and positive predictive value of the different features will be discussed presently. The results should always be compared with the a priori chance of a patient in the defined population having DVT or not. The a priori chance in the present population is 29/164 (17.6%) having CVT, 67/164 (40.8%) having PT, and 68/164 (41.4%) not to have acute DVT.

Table 7:I
Incidence of different results of venography, according to the major complaint of the patient. None of these complaints alters the probability of DVT to be present.

Venogram	A priori chance	Pain	Swelling	Heavy, tired feeling
Normal (68)	41.5%	46 (38.6%)	42 (43.2%)	6 (31.5%)
Calf vein thrombosis (29)	17.6%	27 (22.6%)	7 (7.2%)	2 (10.5%)
Proximal thrombosis (67)	40.8%	46 (38.6%)	48 (49,5%)	11 (57.8%)
CVT or PT (96)	58.5%	73 (61.3%)	55 (56.7%)	13 (68.4%)
Total 164	(100%)	119 (100%)	97 (100%)	19 (100%)

Table 7:II
The influence of the presence of some well known predisposing factors in the patients history, on the probability of DVT to be present.
The reliability interval indicates the incidence of DVT in the imaginary total population of symptomatic patients to be within this range with a probability of 95%.
It appears that only the presence of a known malignancy has a significant influence on the probability of DVT to be present.

History	Venogram				
	Normal		DVT (Reliability interval)		
No peculiarities	28/59	(48%)	31/59	(39-66%)	
< 1 month postoperative	16/45	(36%)	29/45	(49-78%)	
Immobilisation	12/38	(32%)	26/38	(51-83%)	
Previous DVT	7/24	(29%)	17/24	(49-87%)	
Plaster cast	2/7	(29%)	5/7	(29-96%)	
Known malignancy	3/27	(11%)	24/27	(71-98%)	$p < 0.001$
Travellers thrombosis	0/24	(0%)	4/4	(40-100%)	
Femoral vein catheter	0/24	(0%)	4/4	(40-100%)	

Table 7:III
Incidence of DVT in males and females.
It appears that although fewer males than females were admitted to this study, DVT occured in them more frequently ($0.5 > p > 0.1$).

Venogram	♂	♀	
Normal	22 (24-49%)	46 (34-54%)	1 : 2.09
CVT	10 (8-28%)	19 (11-27%)	1 : 1.9
PT	29 (35-61%)	38 (27-46%)	1 : 1.3
Total	61	103	1 : 1.68

Table 7:IV
Occurence of the 'classical signs' of DVT, in a population of 164 symptomatic patients, a distinction is made between patients with a normal venogram and those with DVT. The incidence, specificity and positive predictive values are determined from these figures, together with their 95% confidence interval.

Signs	No	Venogram Normal	Venogram DVT	Incidence	Specificity	Positive predictive value
1. Erythema	62	22	40	40/96 (32-52%)	45/67 (55-78%)	40/62 (51-76%)
2. Cyanosis	7	1	6	6/96 (2-13%)	66/67 (92-99%)	6/7 (42-99%)
3. Venous dilatation	14	1	13	13/96 (7-22%)	66/67 (92-99%)	13/14 (66-99%)
4. Increased skin temperature	63	20	43	43/93 (36-57%)	43/63 (55-79%)	43/63 (55-79%)
5. Edema	133	51	82	82/89 (84-97%)	13/64 (11-32%)	82/133 (54-71%)
6. Calf circumference ≥ 1cm	123	46	77	77/92 (74-91%)	18/64 (18-41%)	77/123 (55-73%)
7. Thigh circumference ≥ 1cm	46	17	29	29/92 (22-42%)	47/64 (61-84%)	29/46 (48-77%)
8. Local pain	122	48	74	74/95 (68-86%)	18/66 (17-40%)	74/122 (52-70%)
9. Homans' sign	60	23	37	37/95 (29-50%)	44/67 (53-77%)	37/60 (48-74%)
10. Firm consistency of calf muscles	54	21	33	33/87 (28-49%)	44/65 (55-79%)	33/54 (47-74%)
11. Lowenbergs sign	4	–	4	4/96 (1-10%)	65/65 (94-100%)	4/4 (40-100%)
12. Temperature ≥ 37⁵°C	40	13	27	27/85 (22-43%)	19/32 (41-76%)	27/40 (51-81%)
13. Pulse rate > 80	54	10	44	44/85 (41-63%)	24/34 (53-85%)	44/54 (69-91%)
14. ≥ 3 positive signs	136	51	85	85/96 (80-94%)	17/68 (15-37%)	85-136 (52-69%)

7.2 Patients history

7.2.1 Major complaints

The major complaints are either pain (119x) or swelling (97x) or both, and occasionally a heavy or tired feeling (19x) (table 7.I). Three patients were not aware of any discomfort but their attending physician thought they had DVT.
The nature of the major complaint does not alter the probability of DVT being present or not. In those patients who indicated pain as their major complaint, DVT was found to be present in 73/119 (61.3%) cases, while it was present in 55/98 (56.1%) of the patients with swelling as a major complaint and in 13/19 (68.4%) of those with a tired and heavy feeling.
Even the occurrence of PT in patients with a heavy feeling (57.8%) is not significantly different from the occurrence of PT in patients without a heavy feeling (38.6%) ($0.5 > p > 0,1$). If we distinguish between CVT and PT, in the former condition pain is the predominant feature, occurring in 27/29 (93.1%) of the cases. In these patients, swelling was a complaint in only 7/29 (24.1%) of the cases. In patients with PT, pain is a less common symptom, it was present in 46/67 (68.6%) of these patients. Swelling however is more frequent in these patients, being a complaint in 48/67 (71.6%) of the cases.

Calf vein thrombosis hardly occurs without tenderness (2/29 = 7%) and PT hardly occurs without calf vein involvement. (CH VI). Nevertheless PT does occur without tenderness in 21/67 (31.3%) of the patients.
This seeming paradox can be explained by the frequent occurrence of asymptomatic CVT when patients are screened with 125 I fibrinogen. These "silent clots" either resolve spontaneously or extend proximally and become overt as a result of the resulting edema[39,62,134,220]. From this point of view, clinically apparent CVT is the early presentation of DVT, while PT with edema is the natural course of subclinical and, therefore, untreated CVT.

```
     ↗ tenderness    →   early recognition and treatment
CVT
     ↘                ↗  spontaneous resolution
       no tenderness →   proximal extension causing edema
                      ↘  unheralded pulmonary embolism
```

7.2.2 Duration of symptoms

The majority of patients were presented within two days (89/176 = 53.2%) or within a week (145/176 = 86.8%) from the onset of their symptoms.
The distribution of CVT and PT does not change with a longer duration of symptoms.

7.2.3 Predisposing factors

In order to investigate the influence of the well known situations predisposing DVT, the probability of DVT in these subgroups is compared to the probability of DVT in a patient with a negative history, being 31/59 (52%) (table 7:II).
The presence of malignancy appears to be the only determinant with a significantly higher rate of DVT, being 24/27 (88.8%) of the cases ($P<0.001$). In contrast to the findings of Kierkegaard [139] a recent surgical procedure has no predictive value with regard to the presence of DVT in this study. Presumably the strict regimen of DVT prophylaxis in our clinic has limited the incidence of postoperative DVT. Prophylaxis was considered to have been desirable in 65 patients and was supplied in 31 of them.

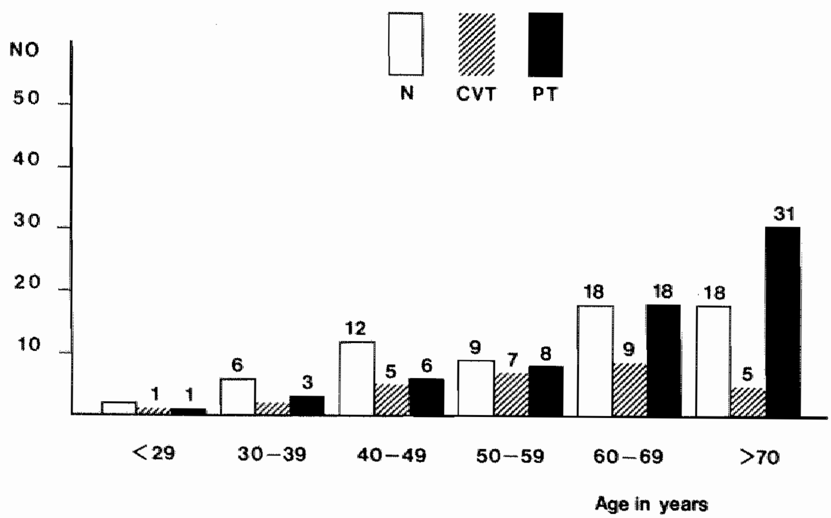
In those patients to whom prophylaxis had been supplied, DVT was present in 17/31 (54.8%), while it was present in 25/34 (73.5%) of those patients from whom it had been witheld (0.1>p>0.05). Four patients with previous femoral vein catheterisation, as well as four patients who had travelled a great distance (Southern Europe-Eindhoven) by motor car without interruption all had PT (Travellers thrombosis). However, these conditions occur too infrequently for these figures to be significant.

7.2.4 Age and DVT

Deep vein thrombosis occurs more frequently with increasing age. In this study the median age was 63 years and 57/167 (34.1%) of the patients were over seventy. Nevertheless DVT does occur in the younger patient and even in childhood. The youngest patient with DVT in this study was 19 years of age. The incidence of DVT in 10 year cohorts is shown in fig 7.1. It appears that although there are few patients in the younger age groups (<40 years) that were admitted to this study, the presence of DVT in these groups does not differ significantly from the incidence in patients over 40 years of age (45% and 63% respectively). Therefore, age as such does not change the likelihood of DVT in the symptomatic patient. The diagnosis of DVT should not be rejected because the patient in question is relatively young.

7.2.5 Sex and DVT

Deep vein thrombosis is often considered to be a womens disease. In this study, the number of females does indeed exceed the number of males; 103:61. When only the patients with DVT are considered, the males are still outnumbered by 57:39. However, the male:female ratio is not the same in the venographical subgroups (table 7:III). In the case of a normal venogram the ratio is 1:2.09, while it is 1:1.31 in the patients with PT. These figures indicate that females are more readily thought to suffer from DVT than males. Once a male patient is thought to be afflicted with DVT, the likelihood of proximal thrombosis is 29/61 (47.5%), while it is only 38/103 (36.85) for females (0.5>p>0.1). Presumably, males and females are affected in equal frequency, but the condition is recognised more often in females.



7.1.

The relation between age in 10 year cohorts and the results of venography being normal (N), calf vein thrombosis (CVT) and proximal thrombosis (PT)

7.3 Physical examination

7.3.1 Colour changes

Erythema, regarded as a "classical" sign of DVT, appears to be rather infrequent, both in patients without DVT; 22/68 (32.3%) as in patients with CVT; 9/29 (31%) and in those with PT; 31/67 (46.2%). The predictive value for DVT being present (40/62 = 64.5%) is almost equal to the a priori chance.
Cyanosis is rarely encountered, and was observed in only 7 patients. When present, however, it is associated with a high specificity of 66/67 (98.5%), and a predictive value of 6/7 (85.7%) for PT to be present.

7.3.2 Venous dilatation

The observation of dilated veins, which sometimes have a high pressure on palpation is another infrequent, but highly specific finding. The phenomenon was observed on the lower leg in only one patient without DVT, and in one patient with CVT. Of the 12 patients with PT showing this sign, it was observed on the lower leg in 9, on the thigh in 1, and on the abdominal wall in 2 patients. The specifity is 66/67 (98.5%), with a predictive value of 13/14 (92.8%).

7.3.3 Skin temperature

Skin temperature is only regarded as a positive sign when the temperature of the symptomatic limb was increased in comparison to that of the unaffected limb. Patients with bilateral warm limbs and 2 patients who previously underwent an amputation were not included. A unilateral increase in skin temperature was observed in 20/63 (31.7%) of the patients without DVT, 8/28 (28.5%) of the patients with CVT and 35/65 (53.8%) of the patients with PT. The predictive value of this sign, 43/63 (68.2%) is only slightly more than the a priori chance.

7.3.4 Edema

Edema was regarded as a positive sign only in those cases where it was more pronounced in the symptomatic than in the unaffected limb. As a consequence, figures on nine patients with bilateral edema and the two amputees are not included. Unilateral edema was present in 51/64 (79.6%) patients without DVT, in 19/24 (79.1%) patients with CVT and in 63/65 (96.9%) patients with PT. The sensitivity of edema is high; 82/89 (92.1%) but its utility is curtailed by the low specificity of 13/64 (20.3%). The predictive value of edema for DVT to be present is 82/133 (62%), which is no different from the a priori chance. The probability of PT in the absence of edema is only 2/20 (10%), but will be higher in the bedridden patient.

7.3.5 Limb circumference

By comparison of the limb circumference, only the more pronounced cases of edema will be recognized, which might improve the specificity. A difference of less than 1 cm. was regarded as insignificant. Six patients with a pre-existent difference in limb girth and the two amputees are not included. A difference in calf circumference of more than 1 cm. was observed in 46/64 (71.8%) patients without DVT, 19/27 (70.3%) patients with CVT and in 58/65 (89.2%) patients with PT. Specificity of this observation is only slightly more than for edema: 18 compared to 13/64 (28.1% and 20.3%) The predictive value is almost equal to that of edema. A difference in thigh circumference is a less common observation, occuring in 17/64 (26.5%) patients without

DVT, 3/27 (11.1%) patients with CVT and in 26/65 (40%) patients with PT. Compared with the presence of edema and the calf circumference, the sensitivity of a difference in thigh circumference is less: 29/92 (31.5%) while the specificity increases: 47/64 (73.4%). The predictive value for PT being present is 26/46 (56.5%).

7.3.6 Local pain

On palpation, pain is indicated most often in the calf region, but sometimes over the course of the popliteal and femoral vein. Pain was indicated by 48/66 (72.7%) patients without DVT, 28/29 (96.5%) patients with CVT and 46/66 (69.6%) patients with PT. Thus, with extension of the thrombotic disease the incidence of local pain becomes a less frequent symptom. The predictive value of pain as such is 74/122 (60.6%). Pain was indicated over the major veins by 21 patients, of whom 17 appeared to have PT, while 4 had a normal venogram. Thus this sign has a predictive value of 17/21 (80.9%).

7.3.7 Homans' sign

This is probably the most renowned of all clinical signs. In the present study however, it was present in 23/67 (34.3%) patients without DVT, 17/27 (58.6%) patients with CVT, and in only 20/67 (29.8%) patients with PT. Therefore, Homan's sign is neither very sensitive (37/95 = 38.9%) nor very specific (44/67 = 65.6%). When CVT is not taken into account, Homans' sign indicates the absence 23/43 (53.4%) rather than the presence of DVT (20/43 = 46.5%).

7.3.8 Consistency of calf musculature

Both an inflammatory reaction and venous congestion could result in a firm consistency of the calf. An increased consistency was observed in 21/65 (32.3%) patients without DVT, 9/28 (32.1%) patients with CVT and in 24/59 (40.6%) patients with PT. Undetermined results were found in 12 patients. The predictive value of this sign (33/54 = 61.1%) is not different from most others.

7.3.9 Lowenberg's sign

Increased pain was indicated on venous congestion by 4 patients, one with CVT and 3 with PT. Thus the predictive value of this sign is 4/4 (100%). However, as this test is rather laborious and extremely insensitive (4/96 = 4.1%), it does not seem to be very useful.

7.3.10 Pulse rate and temperature

Data on the pulse rate and body temperature are available for 117 and 115 patients, respectively. The presence of tachycardia (pulse rate > 80/min) in 44/85 (51.7%) and of fever (temp $>37^{5}$ °C) in 27/85 (31.7%) of the patients with DVT indicates their low sensitivity. The absence of tachycardia in 24/34 (70.5%) and the absence of fever in 19/32 (59.3%) patients not suffering from DVT indicates that these symptoms are not very specific either. Therefore the possibility of DVT should never be rejected on the basis of a normal pulse rate and temperature.

7.3.11 PD score

Finally, one would expect that with an increasing number of positive signs, the Physical Diagnostic Score, the probability of DVT would increase as well. This is indeed the case as is shown in table 7:V. However, it appears that major thrombosis can be present with minor symptoms and that a limb with multiple signs of DVT does not necessarily harbour a thrombus.

Table 7:V

number of positive signs	number of positive venograms	
0	1/3	(33.3%)
1	1/7	(14.2%)
2	9/18	(50.0%)
3	14/29	(48.2%)
4	19/32	(59.3%)
5	31/40	(77.5%)
6	10/19	(52.6%)
7	10/13	(67.9%)
8	1/3	(33.3%)

7.3.12 Conclusions

In this study, the probability of DVT being present in a patient with clinical signs of this condition is 96/164 (58.5%). This figure does not warrant the burden of hospitalization and full anticoagulant treatment. However, this figure is considerable when compared to the probability of DVT in an asymptomatic patient. Therefore there is no reason to neglect the clinical examination, on the contrary: too many patients still suffer from the consequences of undetected and untreated DVT. A sensible policy would be, always to think of the possibility of DVT, but not to treat it without additive confirmation.

7.4 Differential diagnosis of deep venous thrombosis

In several patients without DVT, the diagnosis was still supplied by the venogram, when external compression or previous thrombosis was present. In others, a diagnosis of haematoma or post-traumatic edema was made by exclusion of DVT. The final diagnosis of those patients not suffering from DVT is listed below. In 3 patients no certain diagnosis was made, but their symptoms subsided without specific treatment.

Superficial phlebitis	14
Previous trauma	8
Failure muscle-pump	8
Previous DVT	5
Muscle strain	5
Arthritis condition	5
Haematoma (post-operative)	4
Tumour compression in pelvis	4
Erysipelas	3
Lymfe edema	3
Coup de fouet	2
Resorption fever	1
Abces in calf	1
Popliteal aneurism	1
Post-venographic syndrome	1
Unknown	3

Table 8:I
Observed incidence of characteristic venous Doppler signals in 154 symptomatic patients, arranged according to the result of venography. At the level of the common femoral vein a distinction is made between patients with popliteofemoral and those with iliac vein thrombosis (S = spontaneous, A_1 = compression, A_2 = decompression sound).

Doppler Signal	Venogram				
Posterior tibial vein	Normal (58)	CVT (29)	PT (67)		tot.
S: normal	26	5	5		36
diminished	3	1	4		8
continuous	–	–	1		1
absent	22	22	55		99
other	7	1	2		10
A1: normal	51	18	11		80
diminished	6	4	22		32
loud + dull	0	2	22		24
absent	1	5	10		16
other	–	–	2		2
A2: normal	48	12	4		64
diminished	7	4	10		21
dull, abruptly ending	0	3	27		30
absent	2	10	24		36
other	1	–	2		3
Popliteal vein					
S: normal	52	24	5		81
diminished	–	4	1		5
continuous	–	–	33		33
absent	2	1	24		27
other	4	–	4		8
A1: normal	55	27	5		87
diminished	1	1	34		36
loud + dull	–	–	3		3
absent	1	–	13		14
other	1	1	12		14
A2: normal	55	26	5		86
diminished	1	2	29		32
dull, abruptly ending	–	–	3		3
absent	1	–	18		19
other	1	1	12		14
common femoral vein			p. fem	iliac	tot
S: normal	56	27	23	1	107
diminished	–	–	2	4	6
continuous	–	1	11	19	31
absent	–	–	1	4	5
other	2	1	1	1	5
Aprox: normal	57	26	23	2	108
diminished	–	1	12	13	26
loud + dull	–	–	–	–	–
absent	–	–	1	6	7
other	1	2	2	8	13
Adist: normal	51	19	4	2	76
diminished	3	5	17	5	30
loud + dull	–	–	–	–	–
absent	–	4	14	12	30
unclassified	4	1	3	10	18

VIII Clinical evaluation of the venous Doppler examination

8.1 Introduction

In the course of this study, both venography and a complete Doppler ultrasound examination were performed in 164 patients. In order to maintain the advantage of its simplicity, the Doppler examination was, as a routine, performed with a portable pocket-size apparatus, with an emission frequency of 8 MHz and an audio bandwidth of 300-3500 Hz (Sonicaid BV 102 R). Appreciation of the examination is acoustical and partly tactile. Venous Doppler signals were obtained from three levels, the posterior tibial vein (PTV), popliteal vein (PV) and common femoral vein (CFV). In a small number of patients the saphenous vein (SV) was examined as well.
Each signal was recorded as normal (+), diminished (±), or absent (-). Additionally, specific features such as a dull sounding signal, abrupt ending of the decompression signal, a continuous harsh sounding spontaneous signal or others were described separately. At all levels the signal was compared with the signal obtained from the contralateral limb.
In 12 patients who were unable to adopt a prone position, the augmented signals could not be judged from the popliteal vein, and the S sound could not be judged in 2 of these patients. Five patients with external venous compression and 5 with exclusive signs of previous DVT are excluded from this analysis.
In the remaining 154 patients, the following results were obtained by venography:

normal	58
calf vein thrombosis	29
proximal thrombosis	67

For these patients, the spontaneous and augmented sounds from the different levels will be compared with the venogram (table 8:I and fig. 8:1-3). The predictive values of several characteristically signals are summarized in table 8:II.
At the level of the ankle, both patients with CVT and PT are regarded as having DVT. At the proximal levels, the patients with CVT are classified together with the patients with a normal venogram.

8.2 Posterior tibial vein

8.2.1 Spontaneous sound

At the level of the PTV, a normal S sound was obtained in 26/58 (45%) patients without DVT, and in 10/96 (10%) patients with DVT.The negative predictive value of a normal S sound for DVT not to be present is 26/36 (72%). A diminished S sound was heard in 3/58 (5%) patients without and 5/96 (5%) patients with DVT.
A continuous S-sound was heard in only one patient with DVT. Absence of the S-sound was observed in 22/58 (38%) patients without, and in 77/96 (80%) patients with DVT, accounting for a positive predictive value of 77/99 (77%) for DVT to be present.

In 3 patients the S sound was observed only after a Valsalva manoeuvre, and in 4 others it was "hyperaemic", a description used when the signal was abnormally loud, but with a normal frequency. In 3 patients the signal was unclassified.

8.2.2 Compression sound

A normal compression (A1) sound was obtained in 51/58 (88%) of the patients without and in 29/96 (30%) of the patients with DVT.
The negative predictive value for DVT not to be present in cases with a normal A1 sound is 51/80 (64%). The A1 sound was diminished in 6/58 (10%) patients without, and 26/96 (27%) patients with DVT, accounting for a positive predictive value of 26/32 (81%) for DVT to be present.
A loud and dull sounding A1 sound was exclusively present in 24/96 (25%) patients with DVT, accounting for a positive predictive value of 24/24 (100%) for DVT to be present. Absence of the A1 sound was observed in only one patient without and in 15/96 (16%) patients with DVT, accounting for a positive predictive value of 15/16 (94%) for DVT to be present.
The A1 sound could not be classified in 2 patients.

8.2.3 Decompression sound

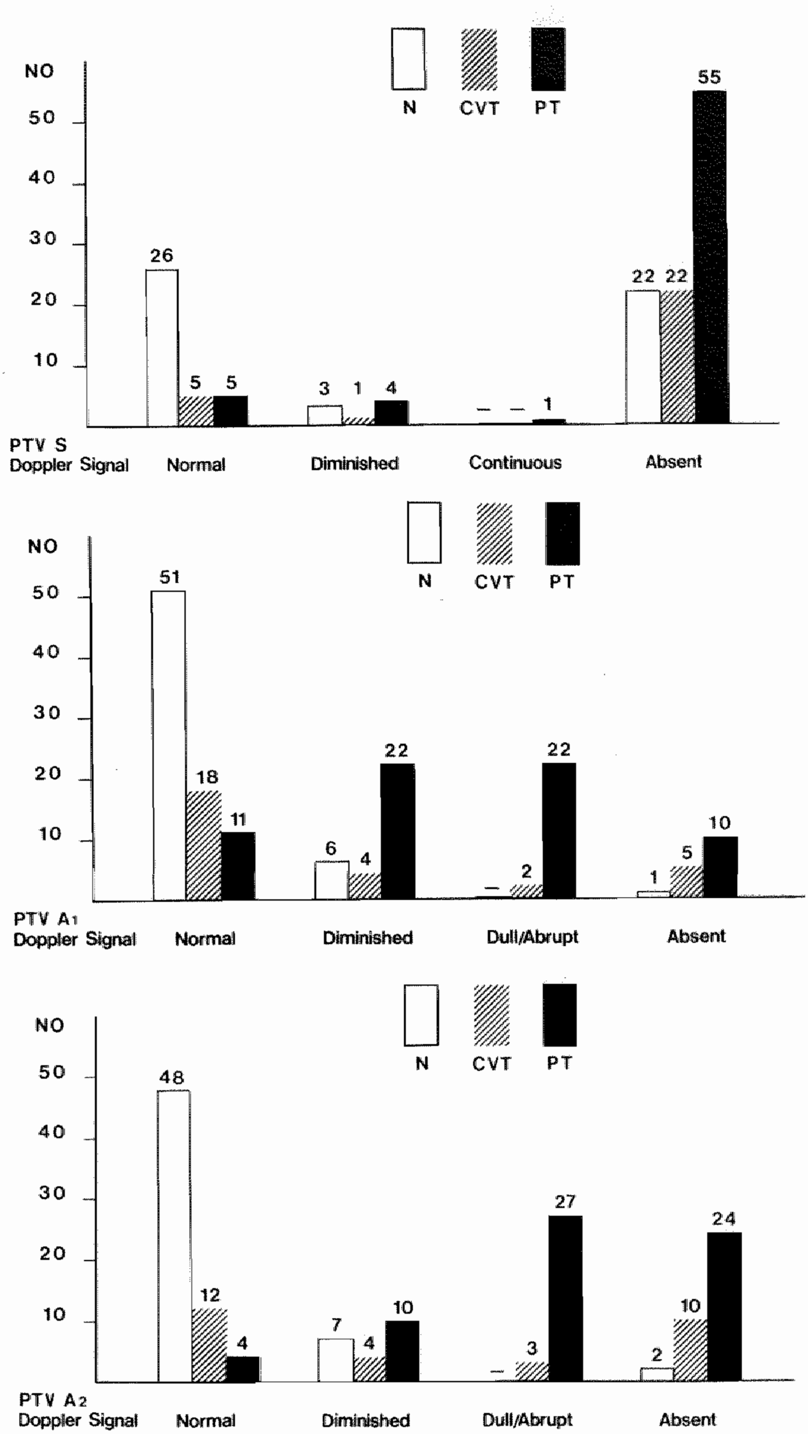
A normal decompression sound (A2) was obtained in 48/58 (83%) patients without and 16/96 (17%) patients with DVT.
The negative predictive value for DVT not to be present in cases with a normal A2 sound is 48/64 (75%). The A2 sound was diminished in 7/58 (12%) patients without and in 14/96 (15%) patients with DVT, accounting for a positive predictive value of 14/21 (67%) for DVT to be present.

Table 8:II
Flow chart of the venous Doppler examination.
Characteristic venous Doppler signals obtained at different levels, their interpretation and the 95% confidence interval of the predictive values.

Level of examination	Quality of the Doppler signal		Conclusion	Predictive N.P.V.	Value P.P.V
Posterior tibial vein	S-sound	Normal	No proximal occlusion (Minor CVT not excluded)	55-86%	
		Diminished	Inconclusive		
		Absent	Inconclusive		68-86%
	A1-sound	Normal	Inconclusive	52-74%	
		Diminished	Probable DVT		50-84
		Loud/dull	Evidence of DVT		86-100%
		Absent	Evidence of DVT		70-99%
	A2-sound	Normal	No proximal occlusion (minor CVT not excluded)	63-85%	
		Diminished	Inconclusive		43-85%
		Loud/dull, abrupt ending	Evidence of DVT		88-100%
		Absent	Evidence of DVT		81-99%
Popliteal vein	S-sound	Normal	No proximal occlusion	86-98%	
		Diminished	Inconclusive		
		Continuous	Evidence of DVT		89-100%
		Absent	Evidence of DVT		76-99%
	A1-sound	Normal	No occlusion proximal to this level	87-98%	
		Diminished	Occlusion at, and distal from this level		81-99%
		Absent	Occlusion at, and distal from this level		66-99%
Common femoral vein	S-sound	Normal	No occlusion proximal to this level	93-99%	
		Continuous	Occlusion at or distal to this level		80-99%

8:1

Occurrence of distinct patterns of the spontaneous (S), compression (A_1) and decompression (A_2) sounds obtained from the posterior tibial vein in symptomatic patients.



A dull and abruptly ending A2 signal was exclusively observed in 30/96 (31%) patients with DVT, accounting for a positive predictive value of 30/30 (100%). Absence of the A2 sound was observed in 2/58 (3%) patients without and 34/96 (35%) patients with DVT, accounting for a positive predictive value of 34/36 (94%) for DVT to be present. The A2 sound could not be classified in 3 patients.
From these figures it appears that the A2 sound is more easily disturbed than the A1 sound both by the presence of DVT as well as by other conditions.

8.3 Popliteal vein

8.3.1 Spontaneous sound

At the level of the popliteal vein a normal S-sound was obtained in 76/87 (87%) of the 58 patients without, combined with the 29 patients with CVT, and in only 5/67 (7%) of the patients with PT. The negative predictive value of a normal S-sound is 76/81 (94%) for PT not to be present. The S-sound was diminished in 4 patients with CVT and in 1 patient with PT.
A continuous, harsh sounding S-sound was heard exclusively in 33/67 (49%) of the patients with PT, accounting for a positive predictive value of 33/33 (100%) for PT to be present.
Absence of the S-sound was observed in 3/87 (3%) patients without and 24/96 (25%) patients with PT, accounting for a positive predictive value of 24/27 (89%) for PT to be present.
Due to problems in positioning the patient, the S-sound could not be judged in 2 cases.

8.3.2 Compression sound

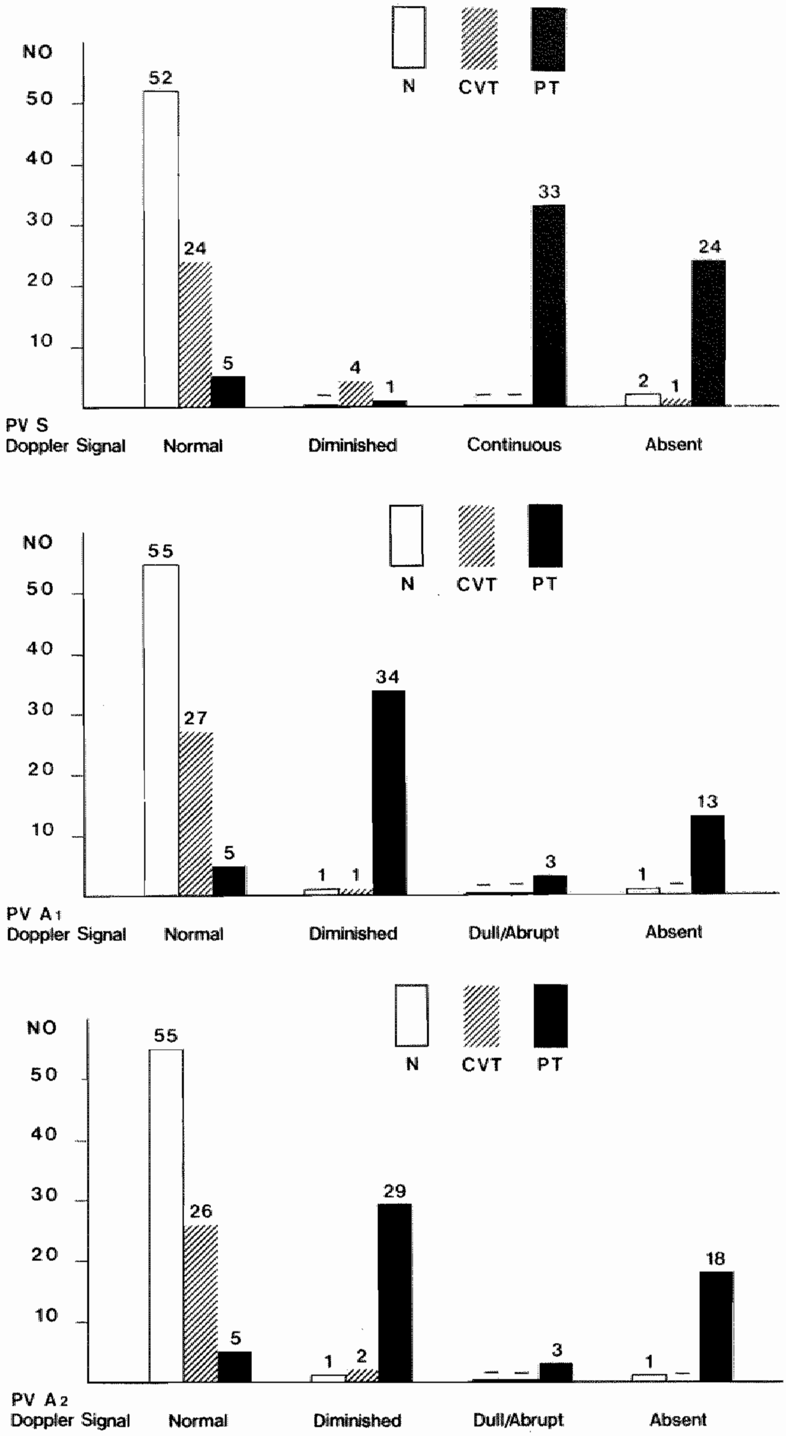
A normal A1 sound was obtained in 82/87 (94%) patients without and in 5/67 (7%) patients with PT. The negative predictive value for PT not to be present in cases with a normal
A1 sound, is 82/87 (94%). The A1 sound was diminished in 2/87 (2%) patients without and 34/67 (51%) patients with PT, accounting for a positive predictive value of 34/36 (94%) for PT to be present.
A loud and dull A1 signal, such a common observation at the level of the PTV, was observed in only 3/67 (4%) patients with PT. Absence of the A1 sound was observed in 1/87 (1%) patient without and in 13/67 (19%) patients with PT, accounting for a positive predictive value of 13/14 (93%) for PT to be present.
Due to problems with positioning of the patient, the A1 sound could not be classified in 12 patients.

8.3.3 Decompression sound

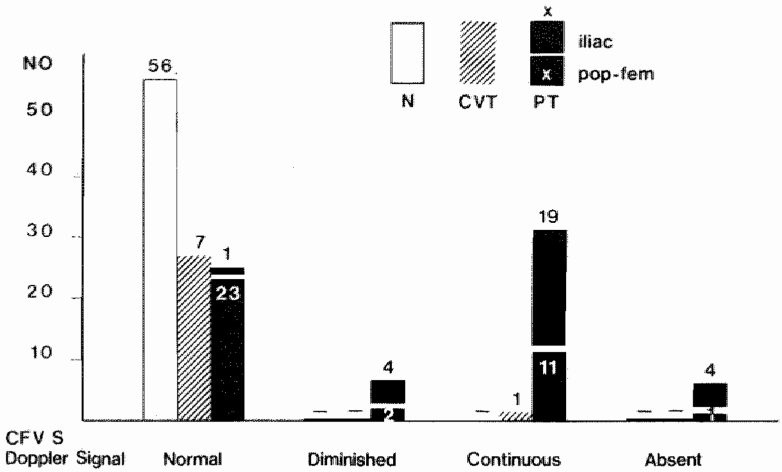
A normal A2 sound was obtained in 81/87 (93%) patients without and in 5/67 (7%) of the patients with PT.
The negative predictive value of PT not to be present in cases with a normal A2 sound is 81/86 (94%). The A2 sound was diminished in 3/87 (3%) patients without and 29/67 (43%) of the patients with PT, accounting for a positive predictive value of 29/32 (91%) for PT to be present.
Just as with the A1 sound, a dull and abruptly ending A2 sound was observed in only 3/67 (4%) of the patients with PT.
Absence of the A2 sound was observed in 1/87 (1%) patient without and 18/67 (27%) patients with PT, accounting for a positive predictive value of 18/19 (95%) for PT to be present. Again the A2 sound could not be classified in 12 patients.

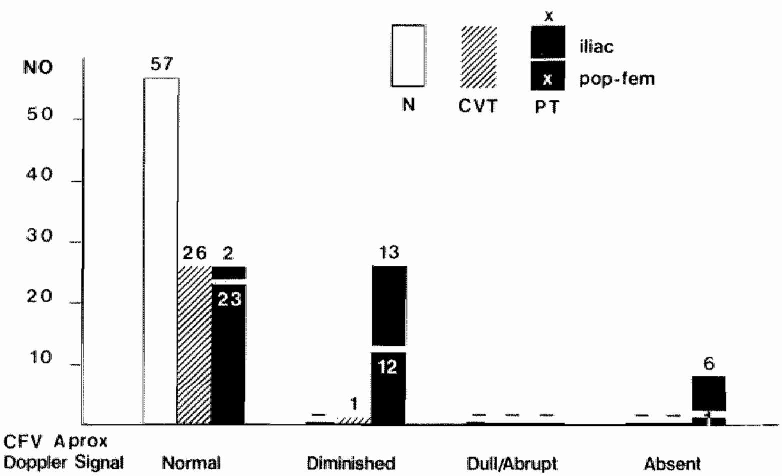
8.2.

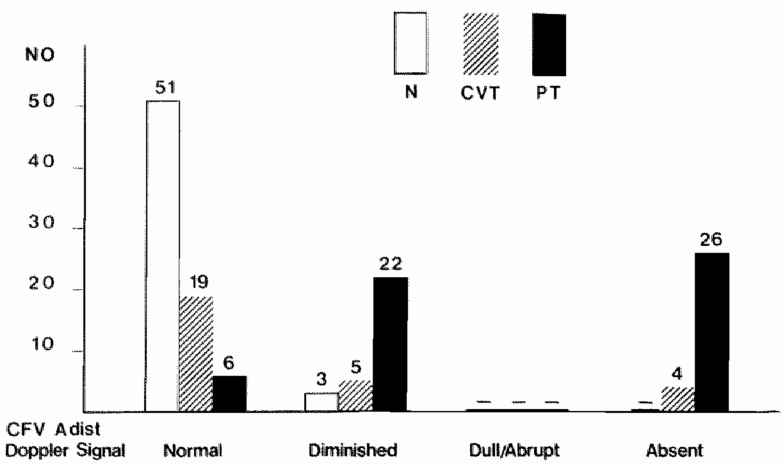
Occurence of distinct patterns of the spontaneous (S), compression (A_1) and decompression (A_2) sounds obtained from the popliteal vein in symptomatic patients.



Occurence of distinct patterns of the spontaneous (S), proximal compression (A prox) and distal compression (A dist) sounds obtained from the common femoral vein in symptomatic patients.







8.4 Common femoral vein

8.4.1 Spontaneous sound

A normal S-sound was obtained in 83/87 (95%) patients without, in 23/38 (61%) of the patients with popliteo femoral (pop-fem) thrombosis and in 1/29 (3%) patient with a non-occlusive clot in the iliac vein. The negative predictive value of a normal s-sound for thrombosis not to be present proximal to this level is 106/107 (99%). A diminished S-sound was heard in 2/38 patients with pop-fem thrombosis and in 4/29 cases of iliac vein thrombosis. Surprisingly, a continuous sound was observed in 11/38 (29%) of the patients with pop-fem thrombosis, while a normal signal would be expected. Presumably this can be explained by the collateral function of the greater saphenous vein in this situation, resulting in a jet stream near to the level where it joins the CFV. A continuous sound was also observed in 19/29 (66%) of the patients with iliac vein thrombosis and in one patient with CVT. In the case of the patient with CVT,this was ascribed retrospectively to the stretching of the vein over the rim of the pecten osis pubis in this emaciated woman. A normal sound was obtained with the hip joint in flexion.
The positive predictive value of the continuous S sound is 30/31 (97%) for PT to be present. Absence of the S sound was observed in only 5 patients with PT. The S sound was not classified in 5 other patients.

8.4.2 Proximal compression sound

A normal proximal compression sound (A-prox) was observed in 83/87 (95%) patients without, in 23/38 (61%) of the patients with pop-fem thrombosis, and in 2 patients with a clot in the iliac vein. The negative predictive value of a normal A-prox sound, for iliac vein thrombosis not to be present, is 106/108 (98%).
A diminished A-prox sound was obtained in the one patient with CVT and stretching of the common femoral vein, in 12/38 (32%) patients with pop-fem, and 13/29 (45%) of the patients with iliac vein thrombosis. The positive predictive value of a diminished A-prox sound is 25/26 (96%) for PT to be present.
Absence of the A-prox sound was observed in 1 patient with pop-fem, and 6 patients with iliac vein thrombosis, accounting for a positive predictive value of 7/7 (100%) for PT to be present.
The A-prox sound could not be classified in 13 patients.

8.4.3 Distal compression sound

A normal distal compression sound (A-dist) was obtained in 51/58 (88%) patients without, 19/29 (66%) of the patients with CVT, in 4/38 (11%) of the patients with pop-fem and in 2/29 (7%) of the patients with iliac vein thrombosis.
The influence of CVT on this test is uncertain. The negative predictive value for PT not to be present is 70/76 (92%). A diminished A-dist sound was obtained in 3/58 (5%) patients without, in 5/29 (17%) of patients with CVT and in 22/67 (33%) patients with PT.
The positive predictive value of a diminished A-dist sound is 22/30 (73%) for PT to be present.
Absence of the A-dist sound was observed in 4/29 (14%) patients with CVT and 26/67 (39%) of those with PT, accounting for a positive predictive value of 26/30 (87%) for PT to be present.
The A-dist sound could not be classified in 18 patients indicating the difficulty of interpreting this test.
Compression sounds do not seem to add any information to the spontaneous signal of the CFV.

8.5 Greater saphenous vein

Examination of the SV was performed in only 53 patients. Normal signals, including the S sound were observed in 8 patients, augmented sounds were present in 21 others, whilst no signal at all could be obtained in 18 patients. The only useful feature was the loud continuous sound of collateral flow, which was observed in 6 patients, who all had PT on venography.

8.6. Final result

Interpretation of the Doppler signal at a certain level is only valid for the adjacent part of the venous system. A careful comparison with the unaffected limb is mandatory. Whenever abnormal signals are observed, attempts should be made to obtain a normal signal by changing the position of the Doppler probe or the posture of the patient. The clinical condition of the leg should be taken into account: in cases with extensive edema, a slightly diminished Doppler signal is considered normal. Additionally, any cause of external compression on the veins should be looked for.
These rules were applied on the flow chart in table 8:II, in order to reach a final conclusion.

Each leg could be classified as one of the following
- normal
- calf vein thrombosis
- proximal thrombosis
- iliac vein obstruction with patent peripheral veins
- inconclusive for CVT, proximal veins normal
- CVT present, but inconclusive for proximal extension

The result of the Doppler examination in 164 patients is compared with venography in table 8:III.

8.6.1 Normal

The venous Doppler signal was considered to be normal in 50/58 (86%) patients without DVT, in 12/29 (41%) of the patients with CVT and in 4/67 (6%) of the patients with (non occlusive) PT. One patient had external compression of the iliac vein and 4 others had signs of previous thrombosis on venography.
The specificity of the Doppler examination is 50/54 (93%) when 4 patients with an equivocal result are not taken into account.
The negative predictive value of a normal Doppler examination is 55/71 (77%) that no acute DVT will be present and 65/69 (94%) that no proximal thrombosis will be present.

Table 8:III
The final conclusion of the venous Doppler examination, related to the result of venography in 164 symptomatic patients.

Doppler	**Venogram**					
	Normal	CVT	PT	EC	Prev. thrombosis	Total
Normal	50	12	4	1	4	71
Calf vein thrombosis	2	8	–	–	–	10
Proximal thrombosis	2	1	60	1	–	64
Iliac vein obstruction	–	–	1	3	1	5
Doubtful CVT	4	4	–	–	–	8
CVT, doubtful proximal extension	–	4	2	–	–	6
Total	58	29	67	5	5	164

8.6.2 Calf vein thrombosis

Calf vein thrombosis was thought to be present in 2/58 (3%) patients without and in 12/29 (41%) of the patients with CVT.
In 8 other patients no definite conclusion was possible with regard to the calf veins, and CVT was present in 4 of these patients. In one patient with CVT, proximal extension was presumed by the Doppler examination.
When 4 patients with an equivocal result are not taken into account, the sensitivity for CVT is 13/25 (52%).
The predictive value of this examination result is 8/10 (80%) that CVT will indeed be present.

8.6.3 Proximal thrombosis

Proximal thrombosis was thought to be present in 2/58 (3%) patients without, in 1/29 (3%) of the patients with CVT, and it was correctly identified in 60/67 (89.5%) of the cases. In one patient iliac vein obstruction was recognized, without indicating the nature of obstruction, and in two patients the presence of proximal extension of CVT was uncertain. If these last 3 patients are not taken into account, the sensitivity for proximal thrombosis is 60/64 (93.7%).
The predictive value of the Doppler examination result is 60/64 (93.7%) for PT to be present.

8.6.4 Iliac vein obstruction

Iliac vein obstruction of undetermined origin, with patent peripheral veins was recognized in 5 patients. In 3 of these patients external compression was revealed by venography, while acute and previous thrombosis was present in the two other cases.

8.7 Conclusions

In patients with iliac vein obstruction, a venogram is needed to reveal its nature, being either thrombotic or external compression.
In the other patients, treatment could have been based on the Doppler examination without venography.
With this policy, a venogram would have been saved in 159 patients. Anticoagulants would have been withheld in 12/29 (41%) patients with minor CVT and in 4/66 (6%) patients with non-occlusive PT. One case of external compression would have had a delay in detection. Four patients would have been treated with anticoagulants without reason. Assuming that minor CVT does not warrant anticoagulant treatment, 150/159 (94.3%) patients would have been treated correctly.

IX Clinical evaluation of Kenoseography

9.1 Introduction

Both Kenoseography and Venography were performed in 171 patients (table 5.3:1). In each patient, venous outflow was determined once with 20 mm Hg, and twice with 40 mm Hg congestion pressure. The venographical results were as follows:

Normal	57
Calf vein thrombosis	29
Proximal thrombosis	74
External compression	5
Previous thrombosis	6

From the test subject study it appeared that the rate of venous outflow which is obtained, depends on the calculation method used. To examine whether different calculation methods would influence the accuracy rate, all Kenoseograms have been reviewed. From each graph, the following items were determined:

- Venous capacity
- Maximal venous outflow
- 1 sec. value
- 2 sec. value
- 3 sec. value
- 1/2 – 2 sec. value

(fig. 4.2:3)

The average and marginal values of these different parameters are summarized in table 9:I and fig. 9:1. Because of the large range of normal values for venous outflow measurement it seemed useful to compare the results of each affected leg with those of the contralateral limb, in order to classify the result as normal or disturbed. For this purpose the following formula has been used:

$$\frac{2 \times (Le - Ri)}{(Le + Ri)} \times 100\% = TI$$

The result of this formula is referred to as the Thrombosis Index (TI).
When the different outflow determinations from patients without DVT are studied, an increasing sampling time results in the same decline in venous outflow as was observed in the test subjects. The 3 sec. value amounts only to 36/61 (59%) of the MVO. In the patients with PT, this decline is less obvious, but the marginal value distinguishing between normal and PT, declines parallel to the normal values.

9.2 Discriminant analyses

Discriminant analyses was applied, according to the BMDP 7M computer programme. *
This programme is designed for problems with equal standard deviations in both groups. To meet this condition, a log transformation was employed to the obtained parameters, except for the Thrombosis Index. A so called score function is obtained, which is a linear combination of the considered variables, such that the scores of patients with and without disease are separated optimally. On cnoosing the marginal value, one has to compromise between sensitivity and specificity.

It should be noted that since the score function was taylored to the present population, the results will be somewhat flattered. Nevertheless this method is valid to determine the optimal combination of parameters. Ideally the obtained marginal values should be tested in a subsequent study. Because of the generally normal venous outflow in patients with CVT, and because of the undue influence of external compression and previous thrombosis, these patients are excluded from discriminant analysis.
Five patients with proximal thrombosis had to be excluded either because comparison with the contralateral limb was not feasible (2x), or because some of the outflow values could not be determined due to movement artefacts in the recordings (3x). Finally, the results of 57 patients without and 69 patients with proximal thrombosis have been applied.

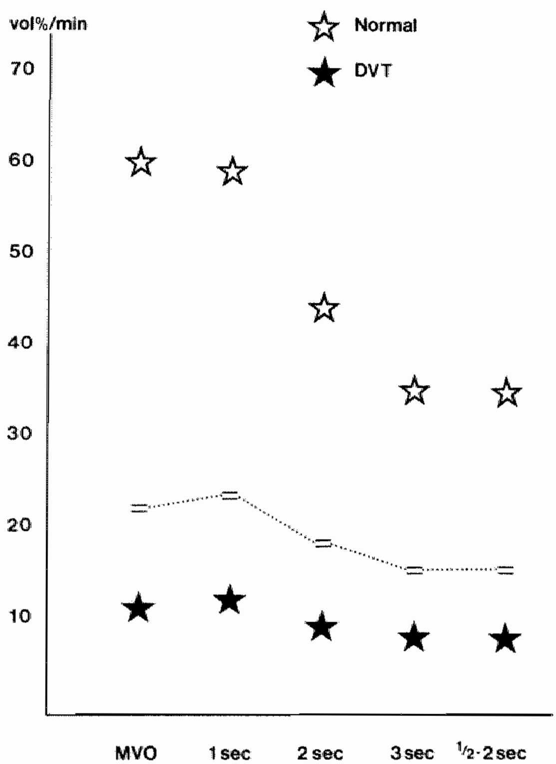
9.2.1 Low congestion pressure determinations

The assumption that the driving force for venous outflow is equal to congestion pressure minus the pre-existent venous pressure, would favour the use of a low cuff pressure. According to this assumption, the ratio of the driving pressure in a normal and a thrombotic limb would decrease with an increase of the cuff pressure.
By this mechanism, the sensitivity for DVT would increase with a decline in cuff pressure. To verify this mechanism, the venous capacity (VC) and maximal venous outflow (MVO) have been determined for both the 20 mm Hg and 40 mm Hg graphs.
In 20 limbs afflicted with thrombosis, no volume increase occured when 20 mm Hg congestion pressure was applied. Presumably the venous pressure exceeded the cuff pressure in these patients. When this phenomenon occurs unilaterally, it can be regarded as diagnostic for DVT. In 5 patients without DVT, however, no tracing could be obtained in either leg, so apparently this low pressure determination is sensitive to DVT, but unfortunately it is sensitive to other influences as well. Of the patients without DVT, 17/52 (32.6%) had an abnormal recording, while 3/49 (6%) of the patients with PT remained undetected. As a result, the accuracy rate is 81/101 (80%) compared with 114/126 (90.5%) for the 40 mm Hg determination, clearly favouring the latter pressure.

*Dixon WJ (Editor in chief); BMDP statistical software, 1981; Univ. of California Press, Los Angeles 1981.

Table 9:I
Average values of different parameters of Kenoseography determined in patients with a normal venogram (57), calf vein thrombosis (28) and proximal thrombosis (69).
The marginal values are determined to distinguish between patients without, and with proximal thrombosis.

Venous outflow		Result of venograhy			
		Normal (SD)	CVT (SD)	PT (SD)	Marginal value
Venous Capacity	vol%	2.50 (1.1)	2.59 (1.5)	0.98 (0.6)	
MVO	vol%/min	61.4 (31.5)	69.9 (44.6)	12.0 (13.3)	22.3
1 sec value	vol%/min	59.6 (27.8)	64.4 (37.2)	12.9 (12.2)	23.7
2 sec value	vol%/min	45.0 (21.6)	48.4 (29.8)	10.2 (9.6)	18.5
3 sec value	vol%/min	36.3 (17.2)	38.1 (22.8)	8.7 (8.0)	15.5
½-2 sec value	vol%/min	36.5 (18.8)	39.4 (25.5)	8.9 (8.7)	15.5



9.1

Average and marginal values of the MVO, 1 sec, 2 sec, 3 sec and 1/2-2 sec values obtained from 57 patients without and 69 patients with proximal thrombosis.

9.2.2 40 mmHg determinations

For the 40 mmHg recordings, all parameters mentioned have been subjected to discriminant analysis. The results are displayed in a two by two fashion in table 9:II.
For the different outflow values almost equal accuracy rates are obtained, being 113/126 (89.7%) to 115/126 (91.3%). It appears that the choice of outflow determination is not critical, as long as the marginal value is adjusted (fig 9:1 table 9:II).

9.2.3 Application of the Thrombosis-Index

For all the outflow determinations, the accuracy is slightly increased by application of the TI, (table 9:II).
In contrast to the outflow determination, a relatively large number of false negative values (6-9 for the different parameters) occur while only 1 – 3 false positive values are observed. In case of a false negative result, either venous outflow in the affected leg is "falsely high" such as in the patients with non-occlusive thrombosis, or the outflow in the contralateral limb is "falsely low". This last situation will occur in patients with bilateral DVT, as was known to be present in 2 patients.
The same principle is applied by direct combination of the outflow values obtained from the symptomatic and asymptomatic limb as shown in fig. 9:2.

In this figure, the discriminant line is determined by the relation between the Thrombosis Index with a marginal value of 68%, and Q, which is:

$$\frac{\text{MVO asymptomatic limb}}{\text{MVO symptomatic limb}} = \frac{200 + \text{TI}}{200 - \text{TI}} = \frac{268}{132} = 2.03$$

As was to be expected, almost identical results are obtained, when compared to those of the Thrombosis Index (table 9:II).

9.2.4 Application of the Hull Nomogram

It is common practice to combine the 3 sec value and the VC in a so called "Hull Nomogram" [188].
Distinction between patients with and without DVT is made by the position in this nomogram, in relation to a discrimination line.
It can be argued though that VC and VO are so closely related that this combined approach will not add to the distinction between normals and DVT (VO = E/R x VC).
In the present material, the BMDP programme did not indicate much additional information to be supplied by combination of outflow and venous capacity (table 9:II).
When the results of the single outflow values are compared with the combined outflow and capacitance results, the accuracy is unaltered for the MVO and 1 sec value while only 1 or 2 additional patients are correctly identified by combination of the VC and 2 or 3 second values.

9.2.5 Biphasic venous emptying

In cases of iliac vein obstruction with patent peripheral veins, a fast volume decline will occur in the first 0.2 sec after cuff deflation (Ch 4.2.9). To avoid this and other possible influences, the MVO was determined by drawing a tangent at 0.5 sec after cuff release. For the same reason, the 1/2-2 sec value was determined. To examine the necessity of this approach, all patients with an apparent biphasic outflow were selected. This phenomenon occured in 3 patients with external compression of the iliac vein and 3 patients with isolated iliac vein thrombosis.

Pathological MVO and 1/2-2 sec values were obtained in all 6 patients. The other outflow values were clearly abnormal in all but one patient.

Apparently this fast volume decline is of such a limited duration and volume (0.2 sec and 0.2 vol% in the test subjects), that the displaced volume hardly interferes with the 1-2 or 3 sec value.

9.3 Application of the results of discriminant analysis on the entire population

It appears that excellent results can be obtained by selecting patients without DVT and with proximal thrombosis. However, we are not interested in a method that will confirm the venographical results, but in a method that can replace venography. Thus we have to look at the patient with a tender and swollen limb, and determine whether or not DVT is involved.

For this purpose the results of discriminant analysis are applied on the entire population (table 9:III).

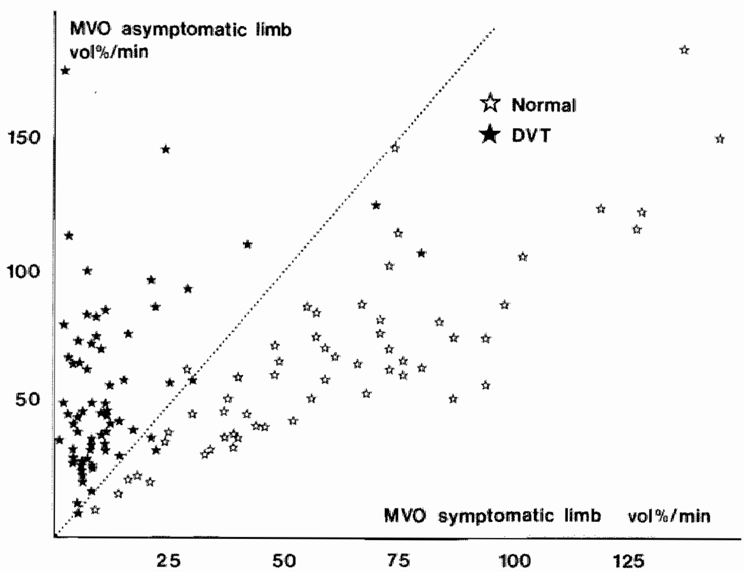
For this purpose, the MVO values of both the symptomatic and the asymptomatic limb were regarded. Only 2/29 (7%) of the patients with calf vein thrombosis were recognised as having a disturbed venous outflow.

Table 9:III
The results of Kenoseography (normal or disturbed) compared with venography, when the results of discriminant analysis are applied on the entire population, including those patients with calf vein thrombosis, external compression and previous thrombosis.

Venography	Venous outflow measurement	
	normal	disturbed
Normal	56	1
CVT	27	2
PT	7	62
External compression	1	4
Previous thrombosis	3	3
total	94	72

Table 9:II
Result of verography compared to various parameters of kenoseography in 57 patients without, and in 69 patients with proximal thrombosis.
For both tests, the result is indicated as normal (N) or proximal thrombosis (PT).
The results of kenoseography can be distinguished in true negative (TN), true positive (TP), false negative (FN) and false positive. The accuracy is the quotient of the correctly identified patients and the total number of examined patients.

Result of Venography	Results of venous outflow measurement									
	MVO		1 sec		2 sec		3 sec		½-2 sec	
	Single parameters									
	N	PT	N	PT	N	PT	N	PT	N	PT
N	52	5	52	5	53	4	53	4	53	4
PT	7	62	8	61	7	62	7	62	9	60
accuracy	90.5%		89.7%		91.3%		91.3%		89.7%	
	Left-right ratio (Thrombosis Index)									
N	56	1	56	1	54	3	55	2	54	3
PT	6	63	9	60	6	63	6	63	8	61
accuracy	94.4%		92.1%		92.9%		93.7%		91.2%	
	Combined Parameters									
	Outflow of symptomatic, compared with asymptomatic limb									
N	56	1	55	2	56	1	54	3	55	2
PT	7	62	8	61	7	62	8	61	9	60
accuracy	93.7%		92.1%		93.7%		91.3%		91.3%	
	Venous outflow, compared with Venous Capacity									
N	52	5	52	5	54	3	54	3	53	4
PT	7	62	8	61	7	62	6	63	8	61
accuracy	90.5%		89.7%		92.1%		92.9%		90.5%	
N	TN	FP								
PT	FN	TP								



9:2

The MVO of the symptomatic, plotted against the MVO of the asymptomatic limb for 57 patients without, and 69 patients with proximal thrombosis. The discriminant line is determined by:
MVO as = 2.03 x MVO s.

As a result, the overall sensitivity for DVT is only 64/98 (65.3%), while it is 62/69 (89.9%) for proximal thrombosis. In this population the specificity is 60/68 (88.2%).
The positive predictive value of an abnormal test result is 64/72 (88.8%) for DVT to be present.
The negative predictive value of a normal test result is 60/94 (63.8%) for DVT not to be present, while it is 87/94 (92.5%) for PT not to be present. With this approach, 34 patients with minor DVT would not have been treated with anticoagulants.
As has been discussed in chapter 3.5, this appears to be safe as long as a subsequent examination is scheduled within a few days. The fact that patients with external compression of their venous system, would have been treated with anticoagulants, while they needed specific treatment, is a more disturbing finding.

9.4 Conclusions

Although a low congestion pressure would seem advantageous, 20 mmHg is inappropriate for venous outflow determination. The choice of the venous outflow calculation method is not critical, as long as the marginal value is adjusted.
A good distinction is obtained between patients with and without proximal thrombosis.
In this study application of the "Hull Nomogram" did not result in a higher accuracy rate than single outflow parameters.
An improvement of the accuracy is obtained by combination of the outflow value of the symptomatic and asymptomatic limb. The method is insensitive for the detection of calf vein thrombosis, while patients with external compression are regarded as having DVT.

X Comparative study between Doppler ultrasound and kenoseography

10.1 Introduction

A combination of Doppler ultrasound and Kenoseography has been proposed by several authors[33, 69, 78, 211]. In 157 venographical controlled patients, both tests have been performed. Because kenoseography does not distinguish between calf vein and proximal thrombosis, those possibilities have to be regarded as one entity in case of an abnormal kenoseogram. The results of these three examinations are presented in a three dimensional table (10:I).

10.2 Normal results

Doppler ultrasound and kenoseography were both normal in 63 patients. Of these patients 48 had a normal venogram. When previous thrombosis is regarded as "no acute DVT" the negative predictive value for DVT not to be present is 50/63 (79%), while it is 61/63 (97%) for PT not to be present. Thirteen patients had a false negative result for both examinations. Of these patients 11 had limited CVT, while two had non occlusive popliteo-femoral thrombosis.

10.3 Abnormal results

In 56 patients, Doppler ultrasound and kenoseography both indicated DVT to be present. Of these patients 55/56 indeed had DVT on venography (1x CVT & 54 x PT), accounting for a positive predictive value of 98.2%. One patient had a popliteal aneurysm, which had displaced the popliteal vein (see case histories). By this combined approach 54/62 (87%) of the patients with PT are recognised as having DVT by both methods, while 60/62 (96.7%) patients with PT are recognised by either or both methods.
Not one of the patients with a normal venogram had abnormal test results for both non-invasive examinations, accounting for a specificity of 56/56 (100%)

10.4 Undetermined results

In *7 patients with a normal kenoseogram* the result of the Doppler examination was equivocal with regard to the presence of calf vein thrombosis. In 4 of these patients CVT was present indeed, while 3 others had a normal venous system.
In 5 patients Doppler examination indicated iliac vein "obstruction" with patent peripheral veins. Kenoseography was normal in 2 of these patients of one of them had external compression and the other had previous iliac vein thrombosis with extensive collaterals. Two out of three patients with an abnormal kenoseogram had external compression of the iliac vein, while the other had acute iliac vein thrombosis with patent peripheral veins.

10.5 Contradictory results

In 23 patients the result of the Doppler examination and kenoseography contradicted each other. In 18 patients kenoseography was normal while the Doppler examination indicated DVT. In 4/18 of these patients, the venogram was normal. Calf vein thrombosis was present in 9/18 and proximal thrombosis was present in 5/18 of these patients.
In contrast, the kenoseogram was disturbed while normal venous Doppler signals were obtained in 5 patients. In these patients PT occurred once, iliac vein compression was observed in one patient and signs of previous DVT were present in 2 others. In one patient a normal venogram was obtained.

10.6 Predictive values

The negative predictive value (NPV) of a normal test result, and the positive predictive value (PPV) of abnormal test results are presented in table 10:II for both Doppler ultrasound, Kenoseography and the combined approach. These figures are derived from the 157 patients in whom all three diagnostic procedures have been performed. The NPV is rather low, in particular for Kenoseography (63%) because of the insensitivity for calf vein thrombosis. The NPV for proximal thrombosis not to be present is acceptable for Kenoseography (92%) and good for Doppler ultrasound and the combined approach (both 97%). The PPV for Doppler ultrasound (93%) and Kenoseography (89%) are acceptable, increasing slightly, but not significantly, to 98% for the combined approach.

Table 10:I
Results of Kenoseography and venous Doppler examination compared with venography in 157 symptomatic patients. In the upper block, all patients with a normal kenoseogram are distinguished according to the results of Doppler ultrasound and venography. In the lower block all patients with an abnormal kenoseogram are selected and distinguished in the same way. (Ec = external compression, prev DVT = previous thrombosis.)

Kenoseogram	Doppler	Venogram						
		Norm	CVT	Pop Fem	Iliac	EC	prev. DVT	Total
Normal	Norm	48	11	2	–	–	2	63
	CVT	2	8	–	–	–	–	10
	pop fem	2	1	4	–	–	–	7
	pop fem il.	–	–	–	1	–	–	1
	isolated il. obstr.	–	–	–	–	1	1	2
	possible CVT	3	4	–	–	–	–	7
	CVT, possible ext.	–	3	–	–	–	–	3
Disturbed	Norm	1	1	–	–	1	2	5
	CVT	–	–	–	–	–	–	–
	pop fem	–	–	23	1	1	–	25
	pop fem il.	–	–	5	23	–	–	28
	isolated il. obstr.	–	–	–	1	2	–	3
	possible CVT	–	–	–	–	–	–	–
	CVT, possible ext.	–	1	2	–	–	–	3
	Total	56	29	36	26	5	5	157

Table 10:II
The predictive values of venous Doppler examination, kenoseography and the combined approach when the results of both tests are in agreement, all related to the result of venography.
Besides the observed figures, the 95% confidence intervals are presented.

	Result of venography				
	Normal	No PT	CVT	PT	DVT
Doppler	54/68 (68-88%)	66/68 (90-99%)	8/10 (44-97%)	57/61 (84-98%)	72/77 (85-98%)
Kenoseography	59/93 (53-73%)	86/93 (85-97%)	–	–	57/64 (79-95%)
Doppler & Kenoseography	50/63 (67-88%)	61/63 (89-99%)	–	–	55/56 (90-99%)

10.7 Specific features

10.7.1 Doppler

Examination with Doppler ultrasound with available pocketsize apparatus has the advantage of its simplicity. This test can be performed anywhere; on the ward, the first aid and outpatient department. The test is without side effects and result is directly available. The extension of DVT can be determined, and distinction is made between thrombotic occlusion of a limb and isolated obstruction of the iliac vein. The major drawback of this method is that the testresult is the subjective impression of the examiner, and experience is required to obtain reliable results.

10.7.2 Kenoseography

When kenoseography is performed strictly according to the rules the test result will be more or less objective. The results should ideally be independent of the examiner, and can be compared with previous or following examinations. With the aid of reference values, the result can be plotted as either normal or disturbed. Drawbacks of this method are that it is more time consuming and is generally performed by a vascular laboratory technician whose presence is required. Although portable apparatus is available, it may be impossible to perform this examination in some patients due to bandaging or traction devices. As appears from this study, there is a low sensitivity for calf vein thrombosis.
Finally, because it is impossible to distinguish between the causes of outflow impairment, the rare cases of external compression will be classified as deep venous thrombosis.

XI Cost effectivenes

When the introduction of a new diagnostic approach is considered, we should see to it that the costs involved are reasonable. Where the diagnosis of DVT is involved, considerable savings are to be expected, because patients with "pseudo-thrombophlibitis", will no longer be treated as if they were affected by DVT.
A cost-effectiveness analysis is made for different diagnostic regimens, applied on the present population.
For this purpose it is customary to apply the fee which is charged to the health insurrance for diagnosis and treatment. The costs of different diagnostic tests and treatment of DVT are listed in table 11:I. Because the fee for non-invasive examination is as yet undecided, the fee for consultation of a specialist was used.
The costs of treatment are calculated to be 7 days in hospital (fl 3150.-) and 6 months of anticoagulant treatment (fl 149.50).
Because hospital managements will have to approve the purchase of new equipment, the budgetary costs are reported as well. For this purpose, radiological equipment is considered to be present in every general hospital, which limits the costs of venography to syringes, contrast and X-ray films (fl 55.-).
For the use of new non-invasive instruments, costs are calculated to be 25% of the initial expense per year, for an estimated number of 100 new patients.
The results of different diagnostic regimens and associated costs are summarized in table 11:II. The consequences of pulmonary embolism and the post-thrombotic syndrome in the untreated patients, and of haemorhage in the inadvertently treated patients are not taken into account. Those patients with external compression (5x) or previous thrombosis are not included.
It is found that improved diagnostic accuracy yields such savings on the treatment of DVT, that any diagnostic regimen is cost effective in comparison to physical examination alone, which is in agreement with the results of others [96, 122].

Table 11:I
The costs of different diagnostic tests and the treatment of DVT, determined both by the fee to the national health insurance and by the actual costs within a budgetary system.

	Insurance fee	Budgetary costs
Treatment	fl 3,299.50	
Doppler	fl 87.50	fl 3.40
Kenoseography	fl 87.50	fl 100.—
Venography	fl 219.–	fl 55.–

The differences in correctly identified patients between the different diagnostic regimens, are not significant.
When compared with clinical examination alone, each other method yields significantly better results ($p<0.001$).

Table 11:II
The accuracy and financial consequences of different diagnostic regimens, determined from the results obtained in 147 symptomatic patients, who have all been examined by all three methods. The costs are considered to be those of the diagnostic test in all patients and the additional costs of treatment in those patients with a positive test result. Eleven patients with CVT were not treated despite the result of venography.

		N	CVT	PT	Diagnosis	Treatment	Costs per patient	Incorrect classified patients, not considering CVT. (95% confidence interval)
Clinical diagnosis	N	–	–	–	–			
	DVT	56	29	62		f485,026.5	f3,299.5	56 (30-46%)
Doppler	N	49	12	2				
	DVT	4	13	59	f12,862.5	f250,762.–	f1,793.3	6 (1.5- 8.5%)
	Other	3	4	1				
Kenoseogram	N	55	27	7				
	DVT	1	2	55	f12,862.5	f191,371.–	f1,389.3	8 (2.3-10.3%)
Doppler + Kenoseogram	N	48	11	2				
	DVT	–	1	54	f19,651.5	f181,472.5	f1,368.2	2 (0.2- 4.7%)
	Other→ven	8	17	6				
Venography	N	56	–	–				
	DVT	–	29 (-11)	62	f32,193.–	f263,960.–	f2,014.6	– (0.0- 2.4%)

XII Discussion

Clinical application of heparin and coumarins has caused a dramatic change in mortality and morbidity due to thromboembolic disease. Anticoagulation, however, is associated with serious side effects of which haemorrhage is the most important. Haemorrhage can be serious enough to warrant hospitalization and may even have a fatal course.
As a consequence it is undesirable either to withhold anticoagulants in patients afflicted with DVT, or to prescribe them in patients whose complaints are not caused by DVT. In relatively young patients with extensive thrombosis of recent onset, fibrinolytic therapy or thrombectomy deserve consideration.
Unfortunately the clinical diagnosis of DVT is neither sensitive nor specific. Many cases of DVT remain undetected until pulmonary embolism ensues, and half of the patients with clinical symptoms of DVT do not suffer from this disease.
We are clearly in need of a test which is simple and safe enough to be performed in any patient with the slightest signs or symptoms of DVT, and yet sufficiently reliable to warrant therapeutic decision making.
Venography is regarded as the most accurate method available. Because of the possible side effects and disturbance to the patient, venography is however unsuitable as a routine examination. Additionally, venography cannot be performed for technical reasons in a number of patients. Reluctance to obtain a venogram from some patients, will diminish the overall sensitivity.
Doppler ultrasound examination and Kenoseography both have the advantage that they are non-invasive, they are not disturbing to the patient and are without side effects. The main limitation of these methods is their insensitivity for calf vein thrombosis.
Kenoseography will not distinguish between DVT and other causes of venous outflow obstruction, while its performance may be impossible for technical reasons.
The main objection against Doppler ultrasound is that experience is required. This, however, should not be a reason to abandon the method, but should rather be an incentive to organise instruction courses in its application.
The question as to whether CVT should be treated with anticoagulants is of crucial importance. Pulmonary embolism has been reported to arise from the calf veins and persistent complaints may occur. Another view is that CVT is a self limiting disease. These thrombi have been shown to resolve spontaneously by the 125 I fibrinogen uptake test and venography. Experience with untreated CVT, obtained in the present study supports this view. In trials in which anticoagulants were withheld from all patients with a normal venous outflow, few patients developed a disturbed venous outflow on subsequent examinations and fatal pulmonary did not occur [127, 281].
The present study supports the view that, in the majority of patients, therapy can be grounded on the results of non-invasive examination. Combination of Doppler and Kenoseography increases the accuracy and will avoid major errors. Whenever one of these methods is not feasible or provides an equivocal result, one can rely on the other method.
In cases of doubt and whenever thrombectomy is contemplated, venography should still be performed. The cost-benefit analysis shows that any of the diagnostic approaches will reduce the number of incorrectly treated patients and is cost-effective. For the hospital budget an accurate diagnosis can be obtained at negligable costs. In those situations where non-invasive examination is not available, venography is to be preferred above clinical examination alone. An algorithm for the patient with clinical symptoms and signs of DVT is presented in table 12:I.

Table 12:I

Algorithm for the approach of patients with symptoms and signs of DVT. Preferentially both venous Doppler examination and Kenoseography are performed in all patients. Venography is required in patients with contradictory results of the non-invasive tests, in patients with isolated iliac vein obstruction and whenever thrombectomy or fibrinolytic therapy is contemplated.
In patients with normal non-invasive test results, an expectant attitude seems justified, but examination should be repeated within a few days. In patients with abnormal non-invasive test results, therapy should be instituted.

Clinical signs/symptoms of DVT
↓
Either Doppler or Kenoseography
preferentially both examinations
↓
One test not conclusive
↓
Add second non-invasive test
↙ ↓ ↘

Either or both normal	Inconclusive or disagreement		Either or both clearly abnormal		
↓	↓		↓		
Expectative, repeat test within 3 days, look for other disease	Venography	←yes	Thrombolytic treatment or thrombectomy contemplated	no→	Hospital admission heparin, coumarin treatment until venous outflow within normal range.

XIII Case histories

The following case histories are presented because they are considered of interest because of pathophysiological, diagnostic or therapeutic aspects. They are by no means representative for the entire population under study.

Case 1

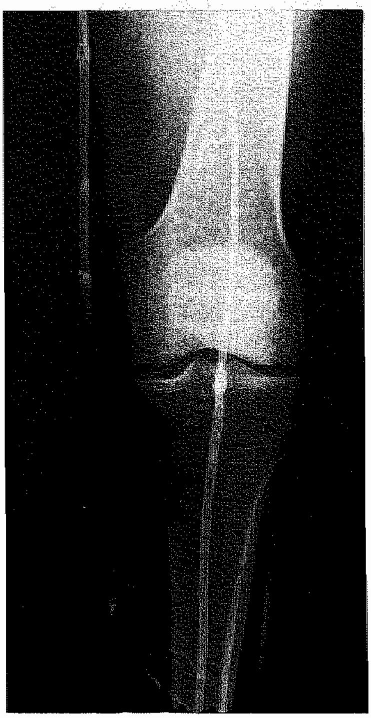
A 45 year old male had been admitted because of colitis ulcerosa. He was treated with bed rest, dietary measures and salazopyrin. During his stay in hospital an uneasy sensation in the left leg and a painful calf developed. A few weeks after the onset of these symptoms he was referred for non-invasive examination of the venous system. At the time of referral, the temperature amounted $38.^{2}$ °C and the pulse rate was 100/min. On physical examination edema, a 2 cm increase in calf circumference and a 0,5 cm increase in thigh circumference was observed. The calf muscles were of a firm consistency, Homans' sign was positive and pain was indicated over the course of the femoral vein. Non-invasive examination clearly indicated proximal thrombosis and venography showed a complete occlusion of the entire deep venous system of the calf and thigh, with only a few superficial veins being present (fig 13:1).
Because of the extent of the disease and because of the risk associated with intense anticoagulant therapy, a thrombectomy was contemplated. Unfortunately, no more than a 10 cm clot could be removed. Postoperatively subcutaneous low dose heparin was administered. After two weeks the patient complained of slight pain on the right calf. On physical examination local tenderness and an increased consistency of the calf was observed. There was no edema, erythema or venous dilatation. Non-invasive examination which had previously been normal for this leg was now obviously disturbed. Venography disclosed a similar result as seen in the left leg before. Because of the recent onset of symptoms, again thrombectomy was attempted, but again with disappointing results. Before this second procedure could be performed, the patient became dyspnoeic with pain on respiration. Pulmonary scanning showed multiple perfusion defects compatible with pulmonary embolism (PE). It was decided to start anticoagulation with coumarins, with strict laboratory control. On long-term evaluation the venous outflow has recovered to normal values. The venous recovery time, however, is impeded with values of 1-2 sec (normal > 15 sec) indicating serious valve incompetence. Despite compression stockings the patient is disabled by a bursting sensation in both legs which makes it impossible to stand for more than 10 minutes. He is unable to resume his work as an engineer, and the prospect for improvement of his complaints are dim.

Comment

In this male patient of relative young age, the symptoms of DVT have not been appreciated sufficiently. Additionally there was reluctance to prescribe the usual anticoagulant therapy. As a consequence he has suffered the untoward effects of pulmonary embolism, and will be disabled by the post-thrombotic syndrome for the rest of his life.
Hopefully the availability of non-invase evaluation will lower the threshold to consider the possibility of DVT. The performance of this entirely innocuous examination on liberal indication might avoid these problems in future patients.

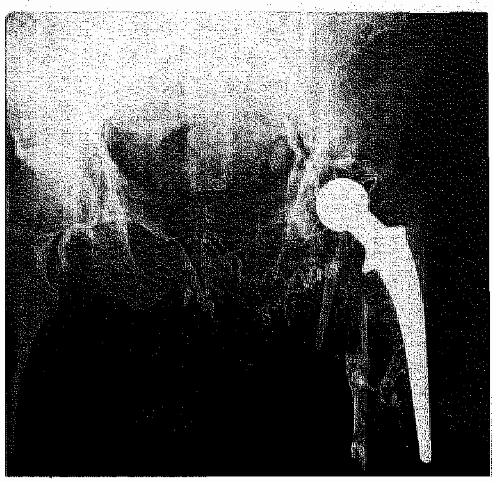
13:1

Complete occlusion of the deep venous system, with only a few superficial veins being patent to provide an outflow tract.



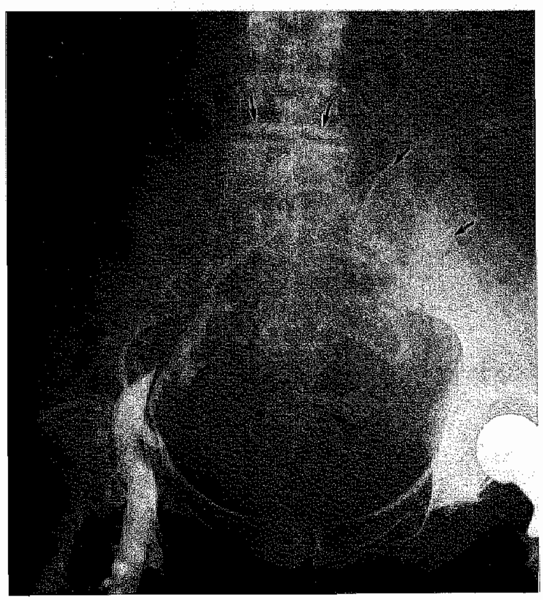
13:2

Primary iliac vein thrombosis after performance of a total hip arthroplasty. The distal part of the femoral vein is patent, and collateral flow through the greater saphenous and pudendal veins can be observed.



13:3

Primary left sided iliac vein thrombosis in a 20 year old female, due to a 'pelvic vein spur'.



13:4

Compression of the right iliac vein, by a 'tumour' which appeared to be the overdistended urinary bladder. Impaired venous outflow was the reason for performing venography in this asymptomatic limb.

Case 2

An 86 year old male patient was admitted because of a left sided femoral neck fracture. Osteosynthesis was performed by means of a dynamic hip screw. Prophylaxis was supplied by daily administration of 500 ml dextran 40 in a 10% solution. Early mobilisation was achieved without weight bearing of the affected limb. After mobilisation excessive edema of the left leg occurred, suggesting deep venous thrombosis.

Physical examination showed a marked edema with an increase in calf and thigh circumference of 3 and 7 cm respectively. The skin temperature was slightly increased. Erythema, tenderness, venous dilatation and Homans' sign were not present. Normal venous Doppler signals and a normal venous outflow were obtained. Venography disclosed an entirely normal venous system. A diagnosis of a sagging hematoma combined with an insufficient muscle pump was made. The patient was treated with supportive bandaging and fysiotherapy. After an uneventful course he was discharged on the 14th postoperative day.

Comment

Fractures of the femoral neck in an elderly patient are notorious for development of DVT, even despite prophylactic measures. Physical examination was consistent with this diagnosis. Additional examination saved this patient from a prolonged hospital admission and the risk of anticoagulant treatment.

Case 3

A 77 year old male was treated for coxarthrosis by a total hip arthroplasty. Prophylaxis was supplied by peroperative administration of 500 ml dextran 40 in a 10% solution, and coumarins were started postoperatively.

On the 10th day postoperatively a rise in temperature to 38 °C occurred, pulse rate was 72/min. On physical examination edema was present in the operated leg. Calf circumference was increased by 2 cm, thigh circumference was equal for both limbs. There was no increase in skin temperature, no erythema or tenderness was present and Homans' sign was negative.

Both Doppler ultrasound and kenoseography indicated proximal thrombosis to be present. Venography disclosed thrombus in the femoral and iliac veins, while the peripheral veins were patent. Apparently thrombus was initiated at the level of the total hip arthroplasty, instead of in the soleal sinusses as usual (Fig 13:2).

The patient was confined to bed, and heparin was added to the coumarins. After mobilisation with a compression stocking, he was discharged in a good condition.

Comment

The history of this patient shows a close resemblance to the previous one. Clinical signs were even less pronounced. Nevertheless, extensive DVT was present in this patient, while it was not in the former one. Presumably extension of the thrombus and PE have been prevented by the instituted regimen in this patient.

Case 4

A 20 year old female was admitted because for few hours she had felt tenderness of the left leg, which was progressively increasing in circumference. There was no history of previous operation or local trauma. She had never before experienced similar complaints. There was no smoking habit, but she did use an oral anticonceptive.

On admission she had a temperature of $37.^{5}$ °C and a pulse rate of 78/min. The entire left leg was swollen with a cyanotic appearance. Skin temperature was decreased, Homans' sign was negative.
Doppler examination indicated femoral and iliac vein occlusion. Kenoseography was abandonned, because the diagnosis seemed obvious. On venography, an iliac vein occlusion was present without peripheral vein involvement (fig 13:3). Because of the recent onset of symptoms and the age of the patient, there was a clear indication for thrombectomy which was performed on the day of admission. On redrawing the thrombectomy catheter, a resistance was present approximately 20 cm proximal to the venotomy. Apparently the thrombus was caused by a pelvic vein spur. Postoperatively she was treated with heparin, after which coumarins were continued for six months. Oral anticonceptives were replaced by an IUD. After an uneventful course she was discharged on the 10th day postoperatively. The Anti Thrombin III level which was determined was in the normal range. Two years after thrombectomy, she is free of complaints. A normal venous outflow was measured by kenoseography.

Comment

Iliac vein thrombosis with patent peripheral veins has been encountered in 4 other patients of relative young age. In all 5 patients there was no apparent reason for the occurrence of DVT, or only minor surgery had been performed. All cases were left sided. These features are characteristic for the pelvic vein spur induced thrombosis. Thrombectomy is a rewarding procedure in these patients.

Case 5

A 74 year old lady was referred 12 days after total hip arthroplasty. Despite prophylaxis by means of low dose heparin, she developed complaints of a thick and rigid leg. She had a pulse rate of 100/min. and a temperature of 37^{6} °C. On physical examination a warm edematous leg was seen with an increased circumference for both calf and thigh. The course of the femoral vein was tender, while Homans' sign was negative. No tenderness, edema or any other sign indicating DVT was present on the other leg.
On Doppler examination, normal signals were obtained from the right leg, whereas those of the left leg clearly indicated proximal thrombosis. Kenoseography revealed an MVO of 12 and 15 vol%/min for the left and right limb respectively, a surprising low value for the "normal" limb. Venography showed the expected DVT on the left side. Because of the low venous outflow a venogram was also obtained from the contra lateral limb. In the right leg a few calf vein thrombi were present, and there appeared to be a "tumour" compressing the iliac vein (Fig. 5.9.:5). This tumour was recognised as being an overdistended bladder by the radiologist. An amount of 2600 cc of urine was evacuated by catheter, after which the MVO of the right leg increased to 29 vol%/min. She was treated by coumarins and supportive stockings.

Comment

This patient is of interest because of the surprising results in the asymptomatic limb. First of all it appears that calf vein thrombosis may be present without clinical symptoms, even if they are specially looked for. Secondly, venous outflow can be disturbed by external compression on the pelvic veins, even by a distended bladder. The TI was seemingly normal in this patient, until the bladder distention was releaved. This parameter should therefore not be used without the outflow being taken into account as well. Similar results have been observed in pregnant women, by recordings before and after delivery.

Case 6

A 68 year old lady had been on holiday in Italy. A few days after return to Holland by automobile, she became aware of an increasing edema of her left leg, which was painful when she stood upright. She had previously been in good health. On admission a little old lady in no apparent distress was seen.

Temperature and pulse rate were not elevated. On physical examination edema of the left leg was observed with a 2 cm increase in calf circumference. A slight erythema was noted and the calf was tender on palpation. Homans' sign was negative.
Non-invasive examination indicated the presence of proximal thrombosis. Venography disclosed thrombosis in the crural veins extending until halfway in the femoral vein. She had an uneventful recovery with bedrest, intravenous administered heparin and subsequenct coumarins.

Comment

This case history demonstrates the thrombogenic effect of prolonged sitting. When one is acquainted with this cause of DVT, it will be easily recognised. One could indeed consider to apply prophylaxis in elderly subjects contemplating to travel large distances by either automobile or aeroplane.

Case 7

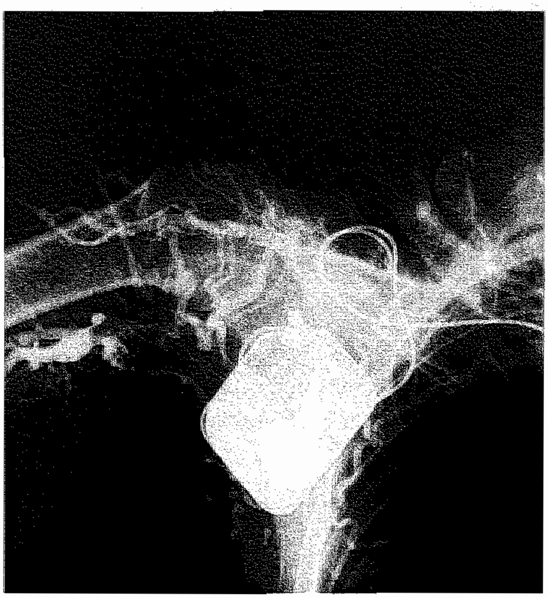
A 45 year old man became aware of a painful right calf 14 days after cholecystectomy had been performed. Prophylaxis had been supplied by intravenously administered dextran 40 in a 10% solution. On physical examination a slight edema was present, without difference in calf circumference. On the medial side over the calf veins an erythematous, warm and locally tender region was present. Homans' sign was positive.
On Doppler examination no spontaneous or augmented sounds were obtained from the PTV. Normal signals were present over the PV and CFV and at all levels of the contralateral leg. Venous outflow amounted 122 and 183 vol%/min respectively, accounting for a TI of 40%.
The patient was treated with analgetics, supportive stockings and he was advised to go for walks, and to sit with elevated legs. Venography which was performed as an outpatient examination disclosed limited calf vein thrombosis (fig 13:5). It was decided to continue the instituted therapy and to withhold anticoagulants. Frequent controls with Doppler ultrasound did not reveal proximal extension of the thrombus and the patients' complaints subsided within a week. On rehearsal of venography four weeks later, complete resolution of the thrombi was observed.

Comment

Apparently anticoagulants can be safely withheld in otherwise healthy patients with limited calf vein thrombosis. As a consequence, both venography and anticoagulants could be safely withheld in patients with normal results of non-invasive examination. With this policy the patient should be instructed to report on progression of symptoms or occurrence of dyspnoe and painful respiration. A shortterm control should be scheduled to detect proximal extension of the thrombus at an early stage should it occur.

Case 8

A 44 year old male sustained a fracture of the left lateral malleolus (type Weber A) by stumbling over the sidewalk. Because of the anatomical position of the fracture he was treated with a plaster cast. No prophylaxis was supplied. On controls, a well fitting cast was seen, the patient had no abnormal complaints. Four weeks after the initial trauma, he became dyspnoeic and had leftsided pain on respiration. He tried an analgetic, which gave temporary relief of the complaints. Two days later haemoptoe occurred and the patient was admitted to the internal ward. On admission temperature was 39 °C and the pulse rate amounted 100/min. He was not aware of anything particular with his left leg. On removal of the cast, a slight edema with a 10 cm increase in calf circumference were observed. There were no other signs or symptoms indicating DVT. On auscultation crepitation was heard dorsally over the lower leftsided lung fields. The thoracic radiogram showed a left pleural effusion and multiple perfusion defects were



13:5

Axillary vein thrombosis, due to the endethelial lesion caused by pacemaker wiring.

13:6

Displacement of the popliteal vein, caused by a traumatic aneurysm of the popliteal artery, following an osteotomy of the tibia. The greater saphenous vein acts as a collateral for the functionally impaired popliteal vein.

present on the pulmonary scan.

Non-invasive examination clearly indicated proximal thrombosis to be present. Venography disclosed complete occlusion of the crural vessels and femoral vein. He was treated by intravenously administered heparin and subsequent coumarins.

Evaluation after one year resulted in a venous outflow of 94 and 107 vol%/min respectively (TI 12.9%). The venous recovery time amounted 1 and 4 seconds respectively, indicating valvular incompetence in the affected leg. The patient is still complaining of a persistent aching feeling.

Comment

A patient with a lower extremity plaster may be walking around, but because the normal muscle pump is not functioning and because gravity impedes venous outflow, this situation should be referred to as "pseudo mobilisation". In particular the combination of a fracture and immobilisation, will render the patient prone to development of DVT. Prophylaxis should be considered. Elevation of the limb and active muscle contraction should be encouraged. This case history also shows that extensive DVT may be present with little or no clinical signs of symptoms.

Case 9

A 59 year old man was seen in the first aid ward because of congestion of the right arm, which had been present for five days. One month before, a pacemaker had been inserted. On physical examination edema and slight cyanosis of the right arm was observed. On elevation of the arms, the veins of the left hand was observed to collapse, which did not occur on the right side. On Doppler examination, a decreased respiratory reaction was noted over the brachial vein, while the augmented sounds were dull and shortened. A continuous bruit was heard in the supraclavicular space. A venous outflow of 10 and 57 vol%/min was obtained from the right and left arm respectively, accounting for a TI of 140%. Venography disclosed an occluded axillary vein, presumably induced by the pacemaker wiring (fig 13:5). He was treated by intravenously administered heparin and subsequent coumarins. The symptoms have gradually subsided.

Comment

Axillary vein thrombosis is relatively infrequent, but the incidence might be higher than usually recognised. The clinical diagnosis is obvious when a proximal vein is completely occluded. In case of PE from unknown origin and in particular in patients with intravenous catheters or pacemaker wiring this possibility should be considered when no other source for PE is found.

Case 10

A 62 year old lady underwent an osteotomy because of genua valga. Prophylaxis was supplied by intravenously administered dextran 40 in a 10% solution and subsequent coumarins. Postoperatively the operated leg became increasingly edematous, red and tender. The temperature rose to subfebrile values and the pulse rate was well above 80 beats/min.

On Doppler examination no S sound was heard over the PTV while the augmented sounds were dull and shortened. In the popliteal space a normal appearing sound was heard far lateral from the usual position and was regarded as collateral flow. Over the CFV and from the contra lateral limb normal sounds were obtained. Venous outflow was 9 and 37 vol%/min respectively accounting for a TI of 122%. Venography, however, disclosed a normal venous system with displacement of the popliteal vein by a large mass (fig 13:6). By subsequent arteriography the presence of a popliteal artery aneurysm was confirmed. The aneurysm has been resected and the circulation was restored by interposition of a venous segment.

Comment

Doppler ultrasound and kenoseography do not detect DVT as such, but can only indicate a disturbed venous flow pattern. They should therefore be combined with a thorough physical examination, and their limitations should be borne in mind. In case of doubt venography remains indispensable to establish the final diagnosis.

XIV Summary

In chapter 1 the inaccuracy of the clinical diagnosis of deep venous thrombosis (DVT) and the importance of an additional test are stressed. The aim of the present study is to evaluate the diagnostic criteria and determine the accuracy of two non-invasive examinations, Doppler ultrasound and venous outflow measurement (Kenoseography) when compared to venography.

In chapter 2 a review is presented of current literature on the various aspects of DVT.

The classical triad of Virchow on the origin of DVT is unchallenged; stasis, alterations in blood composition and endothelial injury are still recognised as the main causes of DVT. With modern technique this triad can be supplemented but not changed.

The anatomy of the venous system is described. Distinction is made between the deep (subfascial), superficial and communicating veins.
Three pairs of crural or calf veins join to form the popliteal vein, which continues into the femoral and iliac veins, which are all indicated as "proximal veins".

The occurence of DVT is clearly age dependant, with an equal frequency in males and females.

The importance of DVT is conditioned by its sequelae, the postthrombotic syndrome (PTS) and pulmonary embolism. The incidence of PTS declines with the application of anticoagulant or fibrinolytic therapy.
Pulmonary embolism is often not heralded by clinical signs of DVT. If untreated, mortality is as high as 30%, declining to 8% with anticoagulant treatment.

Anticoagulant treatment with heparin and subsequent coumarins is the cornerstone in the treatment of DVT. Anticoagulation has caused a dramatic improvement in both morbidity and mortality of DVT. Because of the risk of haemorrhage it should still be used on strict indication only.
In selected cases: younger patients with extensive thrombosis of recent onset, either thrombectomy or fibrinolytic therapy should be considered, to preserve the valvular function.

In chapter 3 the main diagnostic procedures are discussed.
Venography is considered the "Golden Standard" for the diagnosis of DVT. Because it is disturbing to the patient and because side effects occur occasionally, venography is not suitable as a routine examination.

– The clinical diagnosis is neither sensitive nor specific. Thrombosis may occur without clinical signs, and the clinical signs can be caused by many other conditions. Nevertheless physical examination is stil the initial event on the way towards the final diagnosis and should not be neglected.

– It should be borne in mind that many other conditions can be the cause of the clinical signs of DVT. A survey of the possibilities is presented.

– Doppler ultrasound, commonly used for arterial disease, is applied for venous disease as well. Distinctions between arterial and venous blood flow are described.
In a collected series of 1348 patients, the sensitivity for CVT and PT appears to be 46% and 80 respectively. Specificity is 82%, and the predictive value is 70% for a normal and 82% for an abnormal test result.

– A new indication for venous outflow measurement is suggested: Kenoseography instead of Plethysmography.
Registration with strain gauges and impedance measurement is described. Different properties of venous outflow are discussed. Collected series of strain gauge and impedance Kenoseography show almost identical results.
Both methods are insensitive to calf vein thrombosis (56 & 31%) and equally sensitive to proximal thrombosis (95 & 94%). Specifity for both methods is 85 and 94%. The predictive value of a normal test result is 91 and 85%, while it is 78 and 89% for an abnormal result.
No distinction is made between outflow obstruction by DVT or other causes (pregnancy, tumour).

In chapter 4 the results of a test subject study are presented. In 15 test subjects and 29 patients the maximal frequency and duration of the Doppler signal was recorded. In patients with proximal thrombosis, the maximal frequency of the augmented sounds is significantly less (1.07 – 0.63 Khz) when compared with patients without DVT (1.88 – 2.04 Khz) or test subjects (2.76 – 2.52 Khz). The duration of the decompression signal is significantly diminished in case of PT, being 0.38 sec. and 1.7 or 2.2 sec. respectively.

The influence of various conditions on the venous outflow was determined in 10 test subjects. Different calculation methods for the venous outflow provide considerably different results. The 3 sec. value amounts to only 62% of the MVO.
– Venous outflow has a (non-linear) relation with the applied congestion pressure.
– Premature release of the cuff pressure will disturb the accuracy of the determination.
– The rate of cuff deflation determines the venous outflow to a large extent.
– (Hyper) extension of the knee will disturb venous outflow.
– Outflow determination from the ankle instead of the calf, does not increase the sensitivity for calf vein thrombosis.
– Repetitive testing does not increase the venous outflow.
– On a second occasion, venous outflow can be as much as 38% more or less than that recorded on the first occasion.

In chapter 5 the population, study design and statistical aspects are described of a prospective study in 178 patients with a clinical diagnosis of DVT.

In chapter 6 the extension of DVT and the occurrence of different diagnostic criteria are described for 194 available venograms.
For the other examinations, results are always compared with the venogram.

In chapter 7 the results of the patients history and the physical examination are compared with the result of venography. A known malignancy, cyanosis and venous dilatation are the only features with an increased predictive value.

In chapter 8 the acoustically interpreted Doppler signal obtained from the posterior tibial, popliteal and common femoral vein is compared with the venogram in 164 patients.
A dull, abruptly ending augmented signal, a continuous spontaneous signal not being interrupted by respiration and absence of the Doppler signal over the proximal veins appear to be pathognomonic for proximal thrombosis. In the case of normal venous Doppler signals, calf vein thrombosis or non-occlusive proximal thrombosis can still be present. The final conclusion was derived from these observations.
In 7 patients doubt remained as to the presence of calf vein thrombosis. Those patients with a normal venogram were correctly identified in 50/58 of the cases (specificity 86%). Calf vein thrombosis was detected in 13/25 of the cases and suspected in 4 others (sensitivity 52%).
Proximal thrombosis was recognised in 60/64 of the cases (sensitivity 93.7%)

In chapter 9 different parameters were determined from venous outflow tracings of 171 patients.
Discriminant analysis was performed on the results of 57 patients with a normal venogram and 69 with proximal thrombosis.
A congestion pressure of 40 mmHg provides better results than 20 mmHg.
Different venous outflow determinations all result in different average values. As long as the marginal value is adjusted, this does not alter the accuracy. Determination of the Le-Ri-ratio (thrombosis index = TI) provides a slight increase in accuracy.
The criteria obtained have been applied on the entire population. With bilateral MVO – determination, 60/68 patients without DVT were classified as normal (specifity 88%). Calf vein thrombosis was recognised in 2/29 and proximal thrombosis was recognised in 62/69 patients (sensitivity 7-90%).

In chapter 10 the results of Doppler ultrasound and Kenoseography are compared. Contradictory results were obtained in 23 patients. In 18 of these patients the result of the Doppler examination was in agreement with the venogram. The overall accuracy is slightly improved by combination of Doppler and Kenoseography. In patients with contradictory results, venography should be performed.

In chapter 11 the costs of diagnosis and treatment are considered. Considerable savings are obtained by not treating symptomatic patients in whom DVT is not present. Any additionial diagnostic test will decrease the costs of the management of DVT, when compared to the costs of treatment in all symptomatic patients.
Within a budgetary system, treatment of DVT does not charge the budget significantly. An accurate diagnosis can be obtained for maximally fl 100.- per patient.

In chapter 12 the results of this study are discussed. The medical necessity of an accurate diagnosis is obvious. Treatment of DVT without confirmation of the clinical diagnosis seems no longer justified.
Because of the patient's acceptance, non-invasive examination is to be preferred. When these methods are not available, venography deserves preference above the clincal examination alone.
In case of doubt and whenever thrombectomy is contemplated, venography should also be performed.

XIV Samenvatting

In hoofdstuk 1 wordt in het kort het belang van veneuze trombose aangegeven. De onbetrouwbaarheid van de klinische diagnose, en het belang van een goede aanvullende methode worden benadrukt. De doelstelling van dit onderzoek is om in een prospectief onderzoek de diagnostische criteria en de betrouwbaarheid van 2 niet-invasieve onderzoeksmethoden – Doppler ultrageluidsonderzoek en veneuze uitstroommeting (kenoseography)- te bepalen. De resultaten van beide onderzoeksmethoden worden vergeleken met het Röntgen contrastflebogram.

In hoofdstuk 2 wordt een literatuuroverzicht gegeven van enkele aspecten van het trombosebeen. Wat het ontstaan van veneuze trombose betreft is de trias van Virchow nog onverminderd geldig: de oorzaak is steeds te herleiden tot stase, een veranderde samenstelling van het bloed of beschadiging van de vaatwand, als verstoring van het evenwicht tussen stolling en antistolling. Met moderne technieken kan deze trias nader verklaard worden, zonder aan betekenis in te boeten.

De anatomie van het veneuze systeem van het been wordt besproken. Er bestaat een functioneel verschil tussen de diepe (subfasciaal gelegen) en de oppervlakkige venen die door de venae communicantes onderling verbonden zijn. De 6 parallel lopende venen van het onderbeen (kuitvenen) verenigen zich in de vena poplitea, die overgaat in de vena femoralis en vervolgens in de vena iliaca (proximale venen).

Er wordt kort ingegaan op het verschil tussen oppervlakkige thrombophlebitis en diep gelegen phlebotrombose.

Het voorkomen van DVT is duidelijk leeftijdgebonden, met een gelijke incidentie voor mannen en vrouwen.

De betekenis van het trombosebeen wordt bepaald door de mogelijke complicaties: het posttrombotisch syndroom en de longembolie. Het voorkomen van post-trombotische klachten en uiteindelijk het ulcus cruris wordt bepaald door de uitbreiding van de trombus, de ingestelde behandeling en de duur van de "follow-up".

Er overlijden veel mensen aan longembolie, doordat het tevoren bestaande trombosebeen niet als zodanig wordt onderkend. Indien onbehandeld heeft de longembolie een mortaliteit van 30%, dalend tot 8% bij een adequate stollingwerende behandeling. In Nederland overlijden jaarlijks zeker 2500 mensen aan deze aandoening.

Stollingremmende middelen, in eerste instantie heparine en vervolgens een coumarine-derivaat, zijn de hoeksteen in de behandeling van het trombosebeen. Deze behandeling heeft een dramatische verbetering in morbiditeit en mortaliteit teweeggebracht. Bij jonge patienten met uitgebreide trombose van korte duur is een voortvarender behandeling te overwegen. Door chirurgische trombectomie of fibrinolytica zou de functie van de kleppen behouden kunnen blijven, met dientengevolge minder kans op het posttrombotisch syndroom.
Het voornaamste bezwaar van stollingwerende behandeling is het risico van bloedingen die bij 10% van de patienten voorkomen en die een bijzonder ernstige, soms zelfs een dodelijke afloop kunnen hebben. Tijdens de zwangerschap kunnen coumarines een teratogeen effect hebben.

In hoofdstuk 3 worden de belangrijkste diagnostische onderzoeken besproken.
Röntgen contrastflebografie is in de jaren '40 tot ontwikkeling gekomen. Door dit onderzoek kon voor het eerst de klinische diagnose geobjectiveerd worden. De uitvoering en interpretatie van het flebografisch onderzoek worden besproken, alsmede de mogelijke bijwerkingen. Het flebogram wordt algemeen als de "Gouden Standaard" in de diagnostiek beschouwd, maar is vanwege de bijwerkingen niet geschikt als routine-onderzoek.

De klinische diagnose is in tweeërlei opzicht onbetrouwbaar:
– veel gevallen van trombose verlopen subklinisch tot er een longembolie optreedt.
– de klinische verschijnselen die in het algemeen aan trombose worden toegeschreven blijken in de helft van de gevallen op een andere aandoening te berusten.
Er wordt een overzicht gegeven van wat men als de "Klassieke Symptomen" van het trombosebeen zou kunnen beschouwen. De differentiaaldiagnose voor dit symptomencomplex wordt besproken.

Aan het eind van de jaren '60 werd Doppler ultra- geluidsapparatuur ontwikkeld voor de in vivo detectie van stromend bloed. Hoewel de interpretatie van het veneuze Doppler-signaal lastiger is dan van het arteriele signaal, is dit met enige oefening een waardevolle onderzoeksmethode.
Verschillende aspecten van de veneuze bloedstroom en het hierdoor veroorzaakte Doppler-signaal worden toegelicht. Een verzamelstatistiek van 1348 patienten toont een sensitiviteit van respectievelijk 46% en 80% voor kuitvenen en proximale trombose, met een specificiteit van 82%. De voorspellende waarde van een normale uitslag is 70%, en van een afwijkende uitslag 82%.

Het meten van volumevermeerdering (plethysmografie) is een beproefde methode voor het vaststellen van arteriele insufficientie. Het meten van volumevermindering voor de diagnostiek van DVT is hieruit voortgekomen. Voor deze toepassing lijkt de benaming "Kenoseografie" het meest geschikt.
Voor het op indirecte wijze meten van volumeverandering worden rekstrookjes (omtrekverandering), circulaire electroden (weerstands- of impedantieverandering), of met lucht gevulde manchetten gebruikt. Na een periode van veneuze occlusie, door middel van een stuwband om het bovenbeen, wordt de volumevermindering aan het onderbeen gemeten na het opheffen van de veneuze occlusie.
Deze volumevermindering wordt geextrapoleerd naar volumeverandering per minuut. In geval van proximale trombose is deze waarde duidelijk verminderd. De methode is ongevoelig voor kuitvenentrombose. Een verzamelstatistiek van rekstrookjes en impedantie Kenoseografie toont overeenkomstige resultaten.
Dit onderzoek maakt geen onderscheid tussen uitstroombelemmering door trombose of door andere oorzaken (tumor, graviditeit en dergelijke).
De sensitiviteit voor kuitvenen-trombose is laag (56 & 31%), maar voor proximale trombose zeer goed (95 & 94%).
De specificiteit is 85 & 94%.
De voorspellende waarde van een normale uitslag is 91 & 85%, van een afwijkende uitslag 78 & 89%.

In hoofdstuk 4 worden de resultaten besproken van veneuze Doppler signaalanalyse en veneuze uitstroom meting bij proefpersonen.
Bij 15 proefpersonen en 29 patienten werd spectraalanalyse van het Doppler-signaal verricht. De maximale frequentie en de duur van het signaal werden als kenmerk beschouwd.
Bij patienten met proximale trombose blijkt de maximale frequentie van zowel compressie- als decompressiesignaal significant lager te zijn (1,07 – 0,63 KHz) dan van patienten zonder trombose (1,88 – 2,04 KHz) en proefpersonen (2,76 – 2,52 KHz). De duur van het decompressiesignaal blijkt significant minder te zijn (0,38 sec.) dan bij patienten zonder trombose en proefpersonen (1,7 en 2,2 sec.).

Bij een tiental proefpersonen werd de invloed van verschillende factoren op de veneuze uitstroomsnelheid bepaald. Het blijkt dat verschillende berekeningsmethoden, op dezelfde curve toegepast, aanzienlijke verschillen te zien geven: zo bedraagt de 3 sec. waarde slechts 62% van de MVO.

- De veneuze uitstroom neemt, niet lineair, toe met de gebruikte stuwdruk.
- Door de stuwdruk voortijdig weg te nemen, zijn onnauwkeurigheden te verwachten.
- De ontledigingssnelheid van de stuwmanchet heeft aanzienlijke invloed op de veneuze uitstroom.
- Door (hyper)extensie in de knie kan de vena poplitea afgedrukt worden. De benen dienen derhalve steeds geflecteerd te zijn.
- Aan de enkels wordt een lagere uitstroom gemeten dan ter plaatse van de maximale kuitomvang. Deze distale meting heeft echter geen invloed op de sensitiviteit voor kuitvenentrombose.
- Het meerdere malen herhalen van deze meting heeft geen invloed op de veneuze uitstroom.
- Bij herhaling van het onderzoek kan de MVO tot 38% hoger of lager uitvallen dan bij het eerste onderzoek.

In hoofdstuk 5 wordt de opzet en statistische bewerking besproken van een prospectieve studie bij 178 patienten met een klinische diagnose "trombosebeen".

In hoofdstuk 6 worden de resultaten van flebografie besproken.
Van in totaal 194 flebogrammen wordt de uitbreiding van het trombotisch proces beschreven. Het voorkomen van de verschillende diagnostische criteria wordt vergeleken met de uitbreiding van de trombose.

In hoofdstuk 7 wordt het klinisch onderzoek vergeleken met de flebografie.
Gegevens uit de anamnese van de patient bieden weinig houvast voor het stellen van de diagnose.
Pijnklachten en zwelling van het been komen even vaak voor bij patienten met trombose, als bij patienten met een normaal flebogram. Alleen een bekende maligniteit gaat gepaard met een significant hogere kans (24/27 = 89%) op een afwijkend flebogram.
Van het lichamelijk onderzoek hebben alleen cyanose en veneuze dilatatie een grotere voorspellende waarde dan de a priori- kans op trombose in deze populatie. Vergeleken met de asymptomatische patient, is de voorspellende waarde van aanwezige klinische symptomen echter groot. Klinisch onderzoek blijft de basis van de uiteindelijke diagnose.

In hoofdstuk 8 wordt de acoustische beoordeling van het Doppler-signaal op verschillende niveaus van het been (enkel, knieholte en lies), wordt van 164 patienten vergeleken met het flebogram. Een dof klinkend, abrupt eindigend compressie en decompressie- signaal, continue ruis zonder reactie op de ademhaling en afwezigheid van het spontane signaal over een proximale vene blijken pathognomonisch voor proximale trombose.
Indien normale veneuze signalen worden verkregen, is de aanwezigheid van beperkte kuitvenentrombose of niet occlusieve proximale trombose niet uitgesloten.
Op grond van het onderzoek van de verschillende niveaus wordt een uiteindelijke conclusie getrokken. Bij 7 patienten kon geen zekere uitspraak worden gedaan over eventuele kuitvenentrombose. Van de patienten met een normaal flebogram werden er 50/58 juist beoordeeld (specificiteit 86%).
Kuitvenentrombose werd 13/25 maal zeker geacht, en 4x vermoed (sensitiviteit 52%).
Proximale trombose werd 60/67 maal herkend (sensitiviteit 93.7%)

In hoofdstuk 9 wordt de veneuze uitstroom meting vergeleken met de flebografie. Van 171 patienten werden verschillende parameters voor de veneuze uitstrom bepaald. De gegevens van 57 patienten met een normaal flebogram en 69 patienten met proximale trombose werden gebruikt voor discriminantanalyse.
Een stuwdruk van 40 mmHg levert betere resultaten op dan 20 mmHg. De verschillende uitstroomparameters leveren alle andere gemiddelde waarden op.
Zolang de grenswaarde wordt aangepast, heeft dit echter geen invloed op de betrouwbaarheid. De bepaling van het Li-Re verschil geeft een geringe verbetering van het resultaat. De verkregen criteria zijn toegepast op de meetresultaten van de gehele populatie.
Uitgaande van de MVO bepaling van beide benen werden 60/68 van de patienten zonder trombose op het flebogram als normaal beoordeeld (specificiteit 88%). Kuitvenentrombose leverde 2/29 maal en proximale trombose 62/69 maal een afwijkende uitslag op (sensitiviteit 7, respectievelijk 90%). Er wordt geen onderscheid gemaakt tussen uitstroombelemmering door acute trombose, oude trombose of externe compressie.

In hoofdstuk 10 worden de resultaten van Doppler onderzoek en nemen ze uitstroom meting vergeleken. Bij 23 patienten werden tegenstrijdige resultaten verkregen. Bij 18 van deze patienten kwam de uitslag van het Doppler-onderzoek overeen met die van het flebogram. Externe compressie op de vena iliaca wordt gekenmerkt door de combinatie van een gestoorde veneuze uitstroom en normale perifere Doppler-signalen.
Indien Doppler en kenoseografie overeenkomstige uitslagen opleveren, klopt dit in 105/119 (88%) van de gevallen met de uitslag van het flebogram.

In hoofdstuk 11 wordt aandacht besteed aan het kostenaspect van diagnostiek en behandeling. Voor een betrekkelijk geringe meerprijs aan diagnostiek, kunnen geweldige besparingen op de behandeling worden verkregen. Binnen het budgetteringssysteem kan voor maximaal fl 100.- per patient een juiste diagnose worden gesteld.

In hoofdstuk 12 volgt een beschouwing over de resultaten van dit onderzoek. De behandeling van het trombosebeen met anticoagulantia heeft een dramatische verbetering in het beloop van deze ziekte teweeg gebracht. Deze behandeling gaat echter gepaard met een bloedingsrisico.
Gezien de geringe betrouwbaarheid van het klinisch onderzoek lijkt het niet langer verantwoord de patient voor diepe veneuze trombose te behandelen, zonder dat deze diagnose geobjectiveerd is.
Aangezien diagnostisch onderzoek ook bij geringe verschijnselen moet worden verricht, gaat de voorkeur uit naar de niet-belastende, niet-invasieve methoden, zoals Doppler ultrageluidonderzoek en veneuze uitstroom meting.
In geval van twijfel en indien trombectomie wordt overwogen, blijft flebografie onontbeerlijk.

Abbreviations

ATV	anterior tibial vein
BV	brachial vein
CFV	common femoral vein
CVT	calf vein thrombosis
DVT	deep venous thrombosis
EC	external compression
FN	false negative
FP	false positive
FUT	125 I fibrinogen uptake test
IKG	impedance kenoseography
IPG	impedance plethysmography
MVO	maximal venous outflow
NPV	negative predictive value
PE	pulmonary embolism
PPV	positive predictive value
PTS	post thrombotic syndrome
PTV	posterior tibial vein
PT	proximal thrombosis (involving the popliteal vein or any more proximal localisation)
PV	popliteal vein
SKG	strain-gauge kenoseography
SPG	strain-gauge plethysmography
TI	thrombosis index = left-right ratio for venous outflow
TN	true negative
TP	true positive
VC	venous capacity
VO	venous outflow

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Voor de lezer

Uitstel van Executie – A. de Swaan

Vaak zit iemand te lezen met het gevoel dat hij eigenlijk iets anders zou moeten doen. Ondertussen leest hij door, enigszins gejaagd en ook wat heimelijk, omdat hij niet weten wil dat hij iets doet wat hij niet mag. Maar van wie mag dat dan niet?

Er moet blijkbaar nog iets anders, maar niet van iemand anders. Het is de zelfdwang die hem beknelt. Onder zijn krant ligt een rapport in A4 (het formaat van de plicht) te wachten, of een stapel giro's, een kladje met nummers om te bellen en brieven die al lang onbeantwoord zijn gebleven.

In de telefoon-beantwoorder steekt een cassette vol aanspraken op zijn plichtsbesef (maar wie is er ook zo dom om elke opbeller zijn verlangens te laten inspreken op een apparaat dat zwijgt en dus voor de eigenaar al half toestemt?).

Zijn leven is halfvol gelopen met verplichtingen die nooit echt worden uitgesteld, maar van moment tot moment worden vooruitgeschoven en die dus altijd even dringend blijven. De functie van alles wat zo iemand onderneemt is nog-niet-doen wat hij zich voorgenomen heeft. Hij moet eigenlijk altijd wat anders doen dan waar hij net mee bezig is.

Een tijd geleden heeft hij iets toegezegd waar hij nu niet meer onderuit kan. Toen leek het nog zo vanzelfsprekend, een kleinigheid, iets wat niet met goed fatsoen geweigerd kon worden, dat misschien ook wel niet door zou gaan, en als het er toch ooit van komen zou, dan pas over een hele tijd. En dat overkomt hem telkens weer. Zo blijkt al die smetteloos lege tijd die hij nog voor zich waande, wanneer die eenmaal aangebroken is, beduimeld, bekrast en verkreukeld door andermans aanspraken. Altijd is hij in beslag genomen door een klein program van nuttige karweitjes, dringende besognes en verwaarloosde verplichtingen die hem, denkt hij, afhouden van zijn ware genoegens.

Hij schikt zich in dit onverbiddelijk regime, kijkt gehaast de krant in, neemt nog even de supplementen mee, al was het maar om bij te blijven. Dan bladert hij de weekbladen door en leest op dubbele snelheid, want enigszins geinformeerd moet hij toch zijn. Zelfs zijn ontspanning wordt een deeltaak, noodzakelijk onderdeel van de zelftucht.

Het is allemaal nog erger. Wanneer hij eindelijk zijn lopende verplichtingen heeft afgehandeld, is hij helemaal niet opgelucht. Want die beslommeringen zijn niet werkelijke opgave. Er is in zijn leven een hoofdstuk waarvan al het andere hem alleen maar heeft afgeleid.

Hij heeft iets belangrijks en moeilijks te verrichten: een rapport te schrijven, of een voorstel, hij moet een ontwerp maken of een plan indienen. En alle muizenissen hebben hem daar tot nog toe van afgehouden.

Vandaag zal hij daar eindelijk aan beginnen. Hij is achter zijn werktafel gaan zitten. Staat nog even op om zijn tanden te poetsen en besluit, om voor het grote werk helemaal fris te zijn, zijn nagels bij te vijlen en zijn jasje af te borstelen. Dat werkt een stuk prettiger.

Nu is hij helemaal op zijn arbeid ingesteld, staart voor zich uit en ziet dat de plafondlamp het nog steeds niet doet. Dat is een kleinigheid en hij draaft al op met ladder, schroevedraaier en tang om eindelijk die fitting eens te repareren. Dat moest toch nog gebeuren.

Terug aan zijn bureau wordt hij geergerd door de wanorde van papieren. Hij zal dat eens keurig opruimen en voor hij het zelf beseft, is hij het huis al uit naar de kantoorboekhandel om daar een half dozijn plastic mappen in signaalkleuren te gaan kopen. Thuis beplakt hij die met etiketten waarop hij in viltstift heeft geschreven: 'NU', 'VANDAAG', 'URGENT', 'AFHANDELEN', 'METEEN' en 'LOPEND'. Alle stukken worden daarin gesorteerd en de stapel mappen komt in de rechterbovenhoek te liggen met twee bij voorrang te lezen boeken er bovenop tegen het opwaaien.

Nu is er werkelijk niets meer dat hem van zijn opgave kan afhouden op een paar kleinigheden na (vulpen vullen, dropjes kopen, onderweg het avondblad halen en dat nog even doorkijken, een huisgenoot naar de tandarts brengen en op de terugweg de auto laten wassen). Hij is geheel gereed.

Zijn pen zweeft boven het papier, klaar om de eerste ingeving die zich roert aan het papier te spietsen. Zijn hand stokt. Niets beweegt. Het is etenstijd.
Deze treurige gesteldheid kwelt vooral mensen die er wat ambitie en enige pretentie op na houden en die bovendien zelf hun werkzaamheden kunnen indelen. Het is een beroepsafwijking van functionarissen en promovendi, architecten, reclame-makers, illustratoren en van al die anderen die van tijd tot tijd met een werkstuk voor de dag moeten komen, iets dat eigen en herkenbaar is, waarmee zij zich vertonen kunnen en waarop zij worden aangekeken, iets dat hun aanzien in de samenleving bepaalt en waarmee zij zich dus aan hun medemensen uitleveren. Waar arbeidsdwang en vervreemding ophouden, daar verschijnt de werkstoornis. Die kwelling, die ooit een echte mannenkwaal leek, wordt met de emancipatie ook een plaag voor werkende vrouwen.
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Curriculum Vitae.

The autor of this study was born in Amsterdam, in 1954.
He lived in Canberra (Australia) from 1962 till 1964.
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